

ANNALS OF INTERNAL MEDICINE

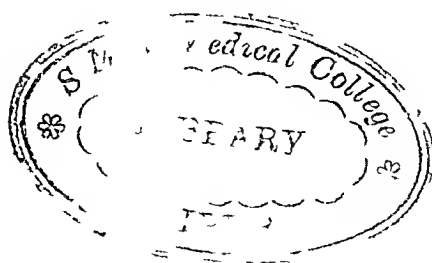
MAURICE C PINCOFFS

Editor

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ANNALS OF INTERNAL MEDICINE

VOLUME 8

JULY, 1934

NUMBER 1

PRESIDENTIAL ADDRESS

By GEORGE MORRIS PIERSON, M D , F A C P , *Philadelphia, Pennsylvania*

It has become one of the customs and traditions of the American College of Physicians each year to accord to the retiring President the privilege of formally addressing the society. As I undertake to fulfill this pleasant obligation I heartily wish that I possessed the sagacity and skill of the late Dr Francis Delafield who, on the occasion of the first meeting of the Association of American Physicians, delivered an address that rivalled in completeness, wisdom and brevity the oft quoted Gettysburg speech of the immortal Lincoln. Dr Delafield's remarks occupy a little short of one page of the transactions of the Association. Although I cannot hope to emulate his achievement I can, however, put your minds at rest with the assurance that I shall do my best not to trespass too long upon your time and patience in what I have to say.

The months that have intervened since our memorable Clinical Session in Montreal have been fraught with events of international as well as national importance. Unbelievable changes of political, social, economic and industrial significance have taken place. Every social group, physicians along with all others, has been profoundly affected. As the result of these altered conditions, the American College of Physicians, together with other organizations, has had to meet unusual and unexpected problems as well as unprecedented economic situations. It is with considerable pride, therefore, that we are able to come before you at this time secure in the knowledge that in spite of the difficult conditions that have existed, the American College of Physicians has thus far come through these turbulent times unscathed.

The losses from the ranks of our Fellows and Associates by death and resignation have been more than offset by the additions to our membership, so that today the total enrollment in the College is 3,100. Furthermore, none of the essential activities of the College has been given up or seriously curtailed. This satisfactory state of affairs is due in large measure to the excellent business judgment, alert watchfulness, and painstaking economy that has been exercised by your Executive Secretary in his efforts to manage the affairs of the College in strict accordance with the wise, far-sighted and

* Read at the Chicago meeting of the American College of Physicians April 18, 1934

conservative policies laid down for him by your Board of Regents and Board of Governors all of whom richly merit your confidence and support I wish to take advantage of this occasion to express to them my personal appreciation of the never-failing interest they have shown in the College and to thank them for the loyal and helpful support they have accorded me, without which your presiding officer would have been unable to direct the affairs of the society with any measure of success

A survey of the addresses of some of my distinguished predecessors as President of the College, discloses the fact that it was not unusual in the past to devote considerable time to a justification of the College and its purposes. Such a discussion today is wholly superfluous in the light of the progress and achievements of the College during the past decade. No more convincing proof is needed that the College has amply justified its existence and now occupies a permanent and unique position among the medical organizations of this continent, than is afforded by an examination of the Roster of our Fellows. It now includes a very great number who, by reason of their outstanding accomplishments in various fields of internal medicine and allied medical sciences, have not only achieved distinction as clinicians and teachers, but have also contributed liberally to the great advances that have taken place in Clinical Medicine during the last quarter of a century.

If time were available it would be both interesting and profitable to enumerate the truly outstanding contributions to the progress of medicine that can be attributed to the Fellows of this College. Moreover, we are particularly fortunate not only in having Fellows who have been and are leaders in medical thought, but in being able to number among our membership a large group of younger Associates, many of whom have already, or soon will have acquired prominence as internists. In these Associates lie the real strength and scientific hope of the College. It is not enough for an organization to number among its members those who have attained distinction, if it would prosper and extend its influence it must be nourished by a steady influx of those who possess the potentialities for future accomplishment.

It has frequently been said that if the American College of Physicians had done nothing else than to inaugurate and successfully conduct its Annual Clinical Sessions, it would have amply justified its existence. With each succeeding year these Sessions have attained greater importance and greater scientific interest. They are unique in that they bring together from all parts of the country, under unusually auspicious conditions, the largest group of men who are primarily interested in all the many and varied aspects of Internal Medicine in its broadest sense.

As popular and successful as these meetings have become, we must not rest content with our present accomplishment. We must be constantly on the alert to find ways and means of improving these Clinical Sessions. Every effort should be put forth to have the outstanding work of the year

that is of interest to clinicians reviewed at our Sessions. In this way large and interested audiences will be assured. It is a well known fact that the prospect of an adequate and discriminating audience is a most effective stimulus to good scientific effort. If we consistently make such audiences available at our meetings, we shall provide an inspiring setting that will soon make those who are doing worthwhile work more eager to present the results of their labors before this College than elsewhere. The hope of having an opportunity to participate in the program of our Clinical Session should prove a constant stimulus to our Associate members. It is not too ambitious to look forward to the day when the gatherings of this College will hold such a conspicuous place among the medical meetings of America that the majority, at least, of the important advances in clinical medicine on this continent will be given to the world through the medium of the American College of Physicians.

It seems not inappropriate at this point to turn away from these questions that involve chiefly the interest and welfare of the College and consider for a moment certain problems that are of fundamental importance to the members of this College as well as to the medical profession as a whole.

Since the world became engulfed in a wave of economic and social unrest associated with widespread financial depression, a number of problems of sociologic, economic and even political importance in connection with medical practice have engaged the attention of the lay public as well as the medical profession of this country. Indeed, in some localities these problems seem to have transcended in importance and popular interest all other aspects of medicine. The term medical economics has sprung into prominence of late and has quite generally been adopted as an expression to designate those problems that involve the various relationships that exist or can arise between physicians, on the one hand, and the public and the state on the other. It is unnecessary to enumerate the manifold problems that fall into this category. Let me hasten to reassure you at this point that your speaker has no intention nor desire to open up the already much debated, although still far from settled problems of medical economics.

The importance of these questions to the country at large as well as to the medical profession is undeniable, since they involve the fundamental problem of the public health upon which rests the happiness, prosperity and the very security of the nation. They involve complicated problems that must be solved and their solution will require mature deliberation and dispassionate as well as sober thought. After a long period of lethargy the medical profession is now aroused to the importance of taking an active interest in these questions, in the final solution of which it is earnestly to be hoped that our profession will take a leading part. Certain it is that if their satisfactory solution is not directed by the medical profession from within, some plan, however unwelcome and distasteful it may prove, will ultimately be forced upon the medical profession from without. Nevertheless, as vital as these issues are, the American College of Physicians hardly

provides the proper forum wherein to debate these moot questions. We are essentially a scientific body dedicated to the advancement of clinical medicine, we represent a group of physicians primarily interested in internal medicine. We are in no sense a cross section of the medical profession of this country. As individuals we are entitled to and should hold definite views on all matters involving the welfare of medicine and the community. As members of our National, County and State societies, we can be afforded ample opportunity to take an active part in moulding both lay and medical opinion on these social and economic questions. In our capacity as Fellows of the American College of Physicians it would seem best for us to see to it that this organization adheres purely to the scientific and educational purposes for which it was created. Let us not dissipate our energy, time and resources in costly investigations of and futile debates, which too often become acrimonious, upon subjects which, however important, do not fall properly within the scope of our activities. This is especially true when there exists a great national medical society which, by reason of its almost universal membership, equipment and organization is the one body best able to deal with these problems and to safeguard and readjust the interests of the physicians and the rights of the public.

Although admittedly, as an organization, we are not properly constituted to deal with the varied aspects of medical economics, there is no escaping the fact that as a group of scientifically trained men we have a real interest in the future development and progress of medicine. It is generally recognized that in medicine, as in virtually every other business and professional activity, marked changes have taken place. In the case of medicine, at least, some of these changes seem to have created situations that are not wholly satisfactory either to the profession or the public. Therefore, it seems timely and not out of keeping with the purposes of this College to review some of the factors that have been responsible for these changes and to consider how medicine may advance in the future in order to correct some of the difficulties that have arisen.

If we look back but a couple of generations we find that the practice of medicine was not surrounded by the difficulties and complexities that beset it today. At that period with few exceptions doctors were general practitioners, few specialists existed and even the outstanding surgeons of the day were not above or averse to the duties of general practice. The family doctor of former days has been so often extolled and his virtues and accomplishments have been so thoroughly praised that it is far from my intention to add to these richly deserved eulogies. Suffice it to point out that the general practitioner of the past was more than a physician, he was a socially minded individual who was an important factor in his community and was regarded with confidence and respect. His word was undisputed in all matters pertaining to health and disease. What he may have lacked in scientific training was more than offset by his understanding of and his keen personal interest in his patients and their problems.

In short, he furnished his fellow beings a medical service that was so generally available and so satisfactory that there was apparently neither the occasion nor the opportunity for the vexing problems involved in medical economics to arise.

Gradually, as the exact sciences were more and more applied to medicine, far reaching changes began to take place and what might be termed the modern era in medicine began. About the end of the last century, with the development of bacteriology, experimental physiology and pharmacology, biochemistry and the other medical sciences, medicine as an art began to decline and the science of medicine came into the ascendancy. With this trend medical teaching was altered, medical courses were lengthened, classes were restricted in size, premedical requirements were increased, scientists began to replace practitioners as teachers and medical students became imbued with the spirit of research and impressed by the importance of the science of medicine. Who can deny the inestimable value of this changed attitude to the progress of scientific medicine. As the result of all this most of the advances upon which modern medical practice is founded took place. In the last fifty years greater progress has been made in all fields of medicine than occurred during the preceding two thousand. But this era of scientific achievement has not tended to develop any widespread interest among medical students in general practice. On the contrary, it has created in many of them an ambition to pursue the more academic and scientific aspects of medicine to the exclusion of practice, while not a few who have gone into clinical medicine have made haste to enter special fields and have exhibited little enthusiasm for the hardships and inconveniences of the general practitioner.

The outcome of this modern trend in medical thought has been that while medicine, established upon a firm scientific foundation, has advanced to an unbelievable degree, the art of medicine has suffered.

The general practitioner, finding it increasingly difficult to keep pace with the rapidly succeeding changes that have been taking place in medical practice, has been gradually superseded either by out and out specialists or by a group of clinicians who by reason of their ultrascientific training have come to look upon patients more as interesting clinical material than as individuals seeking aid for illnesses that are quite as often dependent upon mal-adjustments in their domestic and social environment as upon objective pathological changes and which require for their correction a broad minded, sympathetic viewpoint on the part of a medical advisor. The public has become conscious of this fact. The intelligent layman, fully alive to the incalculable blessings that medical progress has bestowed upon him, is equally aware that as medicine has advanced it has become more impersonal and more specialized. He realizes that a medical examination today is apt to become a costly and formidable procedure devoid of much of the personal interest and understanding in his individual problems that was so conspicuous in the days when the general practitioner held sway. Although

medicine has changed, the psychology of patients has not. For the most part, they still manifest a desire for personal service much the same as they did in the times of our forefathers, in spite of the advances that have taken place in medicine.

One important result of all this has been that the public, finding that broadly trained, socially minded doctors were too often unavailable has gradually drifted away from the general practitioner and turned more and more to specialists and special groups. Where once a single physician cared for a patient and helped solve his problems now many are needed, all regarding the patient from some special angle, none being willing to consider him as a whole. As a consequence, as the prestige of the general practitioner has diminished the cost of medical care has increased. The passing of the general practitioner and the rise of specialism has beyond peradventure been an important factor in the much deplored increased cost of medical service.

Those who are concerned in medical education and the many economic problems that now confront us have gradually become aware of the necessity of altering in some way the training of doctors so that there may be available to the rank and file of the people of this country that to which they are justly entitled, a group of physicians who in a modern way can fill the gap created by the passing of the general practitioner of a former generation.

The pendulum of medical education which moved so far toward the purely scientific side is gradually swinging back. Medical schools everywhere show an encouraging tendency to select as their students not only those who show aptitude for scientific pursuits but those who have the preliminary education, social background and personality to develop into efficient practitioners of broad vision and high ideals actuated by an impelling desire to be of service.

To that end, the training of these men, either before or during their medical school days, should not be limited so strictly to biological and medical subjects, it should include the fundamentals of psychology, sociology and economics so that those who go forth into practice may be socially minded, public spirited citizens capable of taking a leading part in the varied activities of their community and of directing popular thought in all matters pertaining to the health and welfare of the people.

It is generally conceded that less than 5 per cent of medical students are qualified to go into the purely academic or research fields of the medical sciences. Dr. Roger I. Lee has recently shown that 85 per cent of medical practice can be successfully carried out by the family practitioner leaving but 15 per cent that requires the services of a trained specialist. From which it may be deduced that not over 10 or 15 per cent of medical graduates are justified in spending the time and money necessary to equip them as specialists, when the majority of any class are best adapted to general practice and should be trained with that in mind.

The "family doctor" of old is gone forever, but his counterpart must

he developed in the form of a physician possessed of an adequate cultural background, scientifically trained in medicine, thoroughly aware of his personal obligations to his patients and capable not only of treating sickness but also of teaching people how to keep well.

As the result of educational campaigns and propaganda we of the medical profession have created in the public a health consciousness that has made it thoroughly alive to the importance of preventing disease as well as curing it. Today the people expect something more of their doctor than mere care during illness, they require someone competent to advise and direct them in all matters pertaining to their health. In short, the general practitioner of the future must be a "health adviser" as well as a physician. With the control of the great epidemic diseases and other advances in preventive medicine the span of life has been steadily increased, with the result that where once the acute infections played a dominant rôle as a destructive factor now the degenerative diseases incident to advancing years and the wear and tear of life have become the most important causes of disabling illness. Consequently, the "man in the street" who is well aware of these changed conditions, is now chiefly concerned in how to escape cancer, how to avoid becoming a diabetic, how to maintain his kidney function, and how to prevent premature occlusion of his coronary or cerebral circulation and other similar questions. It is upon such pertinent health problems as these that he wants and will in time demand sound medical advice and periodic physical examinations. To meet this need the family health adviser of tomorrow must be alive to the requirements of preventive medicine as applied to the individual. He must be prepared to fill satisfactorily the deficiencies along these lines that unfortunately have existed in the past.

So complex and important have the various methods of diagnosis become that it will never be possible for any individual to become proficient in all branches. Therefore, specialists will always be necessary and, as medicine advances, complicated technical procedures will always be required. In order, however, to have all the studies that may be necessary for any given patient properly correlated and evaluated, there should be some one responsible individual capable of acting as a coordinator. This again is obviously the function of the properly trained modern family doctor. In the future, therefore, a definite move should be made to place the general practitioners in a central position among their professional colleagues.

When a new school of medical practitioners shall have been developed and when such practitioners have firmly reestablished themselves in the minds of the people as their proper health advisers, another important step looking toward protection of the public will take place. As people have sought less and less the guidance of competent general physicians they have acquired more and more the habit of self medication and have fallen victim to the high pressure salesmanship of the drug manufacturers, chain stores, proprietary medicine vendors and a host of other commercialized forms of

advice relative to all varieties of human ills. Fostered by radio broadcasting, popular magazine articles, quasi-scientific lectures and literature and other forms of insidious and alluring advertising, this evil has grown to an enormous extent. It is unnecessary to dwell upon the obvious dangers to health that are brought about by this unintelligent attitude on the part of a thoroughly exploited public. All this has been and is being constantly and admirably done by our national medical society that spares no effort to protect our people. Repeated investigations have shown that each year the American public not only jeopardize themselves but bear an unwarranted economic burden in the vast sums of money which they expend on proprietary remedies and self medication. When this tendency shall have been checked another enormous reduction in the cost of medical care will have been affected. In bringing this about there is no one in such an advantageous position as the modern family physician—an added argument in favor of reeducating the people to look upon such physicians as their legitimate and reliable guides and mentors in all matters pertaining to their well-being.

The members of this College, interested as they must be in the improvement of medical education and the advance of clinical medicine, can do much to further the development of the general practitioner of the future who shall combine the functions of "health adviser" with that of director and coordinator of the medical activities of the people. If in the future, men who embody the qualifications referred to can become the guiding figures in the medical life of our communities, the needs of the public will be adequately cared for and many of the most debated problems of medical economics will be automatically solved.

The modernizing of the family doctor with its attendant curbing of specialization and the inevitable lowering of the cost of medical care, will go a long way toward regaining the confidence of the public in the medical profession. The doctor will be returned to that position of respect, trust and affection which he should occupy in the hearts of the people and, like his predecessors, he will again become an outstanding figure and leader in the affairs of his community and the progress of this nation.

A turning point has come in American medicine. We stand at the crossroads eagerly searching for the guide who can extricate us from the by-ways of uncertainty and point out the highway of progress along which medicine of the future should advance.

The time is at hand when we must look to the more effective control of specialization in medicine, a movement in which the American College of Physicians is bound to play a leading part. Adverse criticism has been directed against the lack of proper regulation of specialization. Control in the sharply differentiated fields of medical practice, such as eye, ear, nose, throat and other specialties, offers little difficulty. The problem becomes more complicated, however, when we attempt to apply it to the broad field

of internal medicine. The solution for the internist may rest in limiting recognition to the subdivisions of internal medicine, as cardiology, gastroenterology, etc.

Your Board of Regents, cognizant of this development, is already active in setting up educational requirements that will be sufficient to guarantee in the future the ability of all successful candidates for Associateship in this College to qualify as internists.

Although the College has made great strides it is destined to further achievements. This is assured by the enthusiasm, ability and distinction of those in whose hands its future rests.

In conclusion, let me again express to you my sincere thanks and appreciation for the honor which you conferred upon me when you saw fit to elevate me to the presidency of the American College of Physicians.

INHIBITORY HORMONES AND THE PRINCIPLE OF INVERSE RESPONSE

By J B COLLIP, F A C P, *Montreal, Canada*

It has been a matter of great interest to those working in endocrinology to note in the case of many laboratory animals and also in the case of many patients, that a state of lowered reactivity, of increased resistance or of actual non-responsiveness may gradually become manifested in those that have been treated for a long period with some glandular extract. Likewise, it has been observed that certain previously untreated animals or patients may be non-responsive to injections of a known potent glandular extract. We have only to think of the failure of the parathyroid hormone to affect appreciably the blood serum calcium of the rabbit or of the patient who is resistant to enormous doses of thyroid extract.

In the extensive study that has been made in our laboratory during the past two years upon the thyreotropic hormone of the anterior pituitary, it was proved abundantly that animals treated for some weeks with this hormone extract became non-reactive to it. Moreover, it was shown that the injection of the blood serum of such non-reactive animals into normal animals caused these latter also to become non-reactive to administered potent thyreotropic extracts. The production of a serum inhibitory to the thyreotropic hormone therefore became a possibility. Extending our study, it was found that such an inhibitory principle could be demonstrated in the blood of the rat, rabbit, dog, goat and horse after treatment for six weeks or longer with adequate amounts of the thyreotropic extract.

Further evidence both of a direct and an indirect character has been obtained which would tend to show that inhibitory substances for various hormones may appear in the blood of animals treated for long periods with different hormone extracts. Thus hypophysectomized rats have become non-responsive to the purified growth hormone (Q extract) in about 40 days. Rats which have been treated with the ovary stimulating placental hormone for long periods, and in which the ovaries have become non-responsive, still respond to the maturity factor contained in anterior pituitary. Likewise, rats rendered non-responsive to the maturity factor of anterior pituitary still respond to placental hormone.

The serum of animals treated for many weeks with the placental hormone has been shown to inhibit the effect of placental extract in the immature female test object.

The serum of a horse treated for three months with the pituitary growth hormone has been shown to antagonize the effect of growth hormone on the hypophysectomized rat.

* Read at the Chicago meeting of the American College of Physicians April 17, 1934
From the Department of Biochemistry McGill University, Montreal, Canada

We have obtained most positive evidence of the presence in the serum of horses treated with certain pituitary extracts of substances inhibitory to the ketogenic effect of anterior pituitary extracts

It is not my purpose in this communication to discuss the details of the experimental evidence which has been obtained to support the theory that inhibitory hormones are produced as a response on the part of the organism to the introduction of excessive amounts of various hormones. I wish rather to enlarge upon the theory itself

The production of serum inhibitory to a specific hormone may be viewed in one of two ways. Either the administered hormone extract is acting as an antigen and the inhibitory substance which can be detected in the blood serum of the treated animal is an antibody, or else the inhibitory substance represents a normal constituent of the blood which under normal conditions is balanced, as it were, against the respective hormone in such a manner as to be masked itself. We prefer this latter view, that the inhibitory substance which is found in the blood of animals after prolonged treatment with some hormone extract is a normal constituent of blood. The response of the organism to chronic injections of hormone would consist then in the increased production of the respective inhibitory principle. This theory may be extended further and one may suppose that for each hormone, or at least for many hormones, there exists an opposite, an anti- or inhibitory principle

We have adopted as a working hypothesis the view that anti-hormones, perhaps better called inhibitory principles, are present in the normal subject. This broad principle is particularly attractive since it may be used to explain such things as the great difference in the responsiveness of different species to hormones as well as minor variations in responsiveness within a species. The theory is not without attraction from the clinical side, since it suggests the possibility that any supposedly hypo-hormone state may just as well be a hyper-inhibitory hormone condition or an imbalance between the hormone and its respective inhibitory principle. If one pictures a hormone and its respective inhibitory principle as a complex and views this complex as a "buffer," then one can introduce a quantitative factor in relation to the level of this complex and one species of animal can be sought in which the "buffer" is normally at a low level and others will be found in which the "buffer" is at a much higher level.

In view of the fact that there are many examples of extreme variation in the response of an individual of one species to administered hormone as compared to the response of an individual of another species similarly treated, I was led to postulate in my Welch lecture¹ a few weeks ago, the theory of inverse response.

The principle of this theory can be illustrated by a specific example.

The pituitary of the guinea pig as compared with that of the rat contains relatively very little of the thyreotropic principle, the thyroid of the guinea pig as compared with that of the rat is relatively inactive, the metabolism

of the guinea pig is at a lower level than that of the rat, the guinea pig is exceedingly sensitive to administered thyreotropic hormone, while the rat is extremely resistant. However, the hypophysectomized rat is exceedingly sensitive to this hormone.

The principle of inverse response of which the above is an excellent example may be stated as follows:

“The responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the individual's own gland.”

It is possible to find numerous examples which indicate the very general application of this principle in endocrinology, and as an independent theory it can stand alone. We have been interested, however, in linking the theory of inverse response with the theory of anti-hormones. If one does this then one of the most important implications of the theory is that the level of a hormone is related directly to the level of the corresponding anti- or inhibitory hormone. The demonstration of a hyper-hormone state associated with lowered responsiveness to administered hormone implies the co-existence of a hyper-inhibitory hormone state. One might here draw an analogy between the highly buffered solution which is sluggish in regard to pH change on addition of small amounts of acid or alkali and the hormone resistant animal which is, as it were, well buffered by a high level both of hormone and respective inhibitory principle in its system.

That the effect of a small dose of a hormone will be greater when the existing concentrations of hormone and anti-hormone circulating are small than when they are already large will not be regarded as surprising. In many cases of physiological antagonism between drugs, it is known that the *ratio* between the concentrations of the two antagonists determines the physiological effect, whatever the actual amounts, this has been shown for the interaction of atropine and pilocarpine on salivary secretion,² of atropine and acetyl choline on the frog ventricle,^{3,4} of adrenalin and ergotamine on the rabbit uterus,⁵ and elsewhere. The *ratio* will obviously be more disturbed by a given *amount* of hormone when the quantities of hormone and anti-hormone present are initially small.

CLINICAL APPLICATIONS

The clear-cut demonstration of the production of inhibitory substances in the serum of animals for certain hormones with which the experimental animals have been treated should provide occasion for the serious consideration of those effects of a similar nature which may be produced in patients injected with certain glandular extracts over a long period of time. One sees, for instance, the possibility of the clinician in his endeavor to correct a hypoglandular state actually adding to the gravity of the condition by causing an overproduction of inhibitory principle as a result of too persistent treatment.

While the results of these recent investigations in the laboratory suggest that many dangers may attend the clinical use of glandular extracts, nevertheless they point the way to new applications. If the general principles established by the experimental work are applicable to the human subject, then the possibility must be considered of producing inhibitory hormones in an active way in the system of the patient, or of raising the level of these in a passive way by the use of active extracts of inhibitory sera, the latter produced from horses injected over long periods with adequate amounts of the purified hormones.

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LYMPHOSARCOMA AND HODGKIN'S DISEASE BIOLOGIC CHARACTERISTICS *

By SOLOMON GINSBURG, M D , *New York, N Y*

FOR more than half a century after Hodgkin¹ first described the disease that now bears his name, no sharp line of demarcation was drawn between lymphosarcoma and Hodgkin's disease. Indeed, the two names were considered synonymous by the overwhelming majority of competent investigators of this baffling problem².

In 1893 Kundrat of Vienna recorded a study of 50 cases of lymphosarcoma in which the following tissues and organs were involved: lymph glands, skin, subcutaneous tissues, muscles, breasts, bones, dura, tongue, palate, pharynx, tonsils, larynx, trachea, bronchi, lungs, pleura, thyroid, thymus, pericardium, vena cava, esophagus, stomach, duodenum, jejunum, ileum, cecum, rectum, peritoneum, mesentery, and omentum.

Based principally upon a gross anatomic study of these 50 cases and 100 allied cases, Kundrat³ sought sharply to differentiate lymphosarcoma from Hodgkin's disease on the following grounds:

| <i>Lymphosarcoma</i> | <i>Hodgkin's Disease</i> |
|---|--|
| 1 Invades the capsule of lymph glands | 1 Does not invade the capsule of lymph glands |
| 2 Invades and infiltrates neighboring tissues | 2 Does not invade or infiltrate neighboring tissues |
| 3 Obliterates normal structure of the lymph glands | 3 Does not obliterate normal structures of the glands |
| 4 Extension regional, from one group of lymph glands to another or from one lymphoid area to another. Metastases by way of the blood stream are absent or very rare | 4 A systemic disease from the outset like leukemia |
| 5 Infiltration of hollow viscera by direct extension from involved lymph glands or involved lymphatic channels | 5 Involvement of viscera through blood or lymph channels by the unknown agent of the disease |
| 6 Invasion of hollow viscera causes dilatation of lumen, never constriction | 6 Involvement of hollow viscera causes constriction of lumen |
| 7 Rarely invades bone | 7 Frequently invades bone |
| 8 Invasion of liver and spleen nodular | 8 Invasion of liver and spleen diffuse |
| 9 Persons between the ages of 25 to 55 most frequently affected | 9 Younger individuals more frequently affected |
| 10 Male sex twice as frequently affected as females | 10 Female sex more frequently affected |
| 11 Tuberculosis of the lungs rarely present | 11 Tuberculosis of the lungs frequently present |

The histological description of lymphosarcoma given by Kundrat was limited to the following single paragraph: "As to the histological structure, I have nothing new to add. Lymphosarcomas are characterized by their

* Received for publication April 4, 1934

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reticular stroma and embedded lymphoid cells. It must be emphasized that the lymphosarcomatous tissue does not resemble normal reticular lymphoid tissue. The typical or normal tissue is replaced by atypical stroma with a variable amount of fibrosis and hypertrophy and hyperplasia of cells which deviate from the normal type."

A careful analysis of this histological description probably explains the reason why Kundrat failed sharply to differentiate lymphosarcoma from Hodgkin's disease on the basis of microscopic structure as he did on gross anatomic considerations. A comprehensive survey of the literature until the time of Kundrat's publication fails to reveal in the great majority of outstanding studies on lymphosarcoma and Hodgkin's disease any distinctive microscopic features by means of which these two diseases could be sharply differentiated from one another.

A definite microscopic differentiation of lymphosarcoma from Hodgkin's disease, which occasionally was met with in the literature, was first strongly emphasized shortly after Kundrat's publication by Paltauf² of Vienna, and within the next few years it reached its finished form in the writings of Carl Sternberg⁴ of Vienna and of Dorothy Reed⁵ of Baltimore.

Based upon a careful microscopic study of 15 cases clinically diagnosed pseudoleukemia or Hodgkin's disease, Sternberg formulated the following differential diagnostic points between lymphosarcoma and Hodgkin's disease.

| <i>Lymphosarcoma</i> | <i>Hodgkin's Disease</i> |
|---|---|
| 1 Invades capsule of lymph gland | 1 Does not invade capsule of lymph gland |
| 2 Invades neighboring tissues | 2 Does not invade neighboring tissues |
| 3 Abundance of atypical lymphoid cells No endothelial hyperplasia | 3 Abundance of large endothelioid cells with an admixture of lymphoid and plasma cells |
| 4 Characteristic uninuclear and multinuclear giant cells absent | 4 Characteristic uninuclear and multinuclear giant cells always present |
| 5 Absence of giant cells and endothelioid cells in the blood and lymph sinuses | 5 Presence of large number of giant cells and endothelioid cells in the blood and lymph sinuses |
| 6 Absence of Langhans giant cells | 6 Presence of Langhans giant cells |
| 7 Absence of caseation necrosis | 7 Frequent presence of caseation necrosis |
| 8 Tubercle bacilli absent | 8 Tubercle bacilli frequently present |

The differential diagnostic features between lymphosarcoma and Hodgkin's disease drawn by the Viennese pathologists gained immediate acceptance in the scientific medical world. The only phase that met with prompt dissent by a number of competent students of this problem was the rôle of the tubercle bacillus in the etiology of Hodgkin's disease. One of the foremost among these dissenters was Dorothy Reed of Baltimore, whose classical description of Hodgkin's disease has received widespread and well-merited recognition in the English speaking world.

Accepting in the main Sternberg's histologic description of Hodgkin's disease and stressing in addition the frequent presence of eosinophiles, Reed correctly pointed out that Langhans giant cells, caseation necrosis and tubercle bacilli are an associated condition in Hodgkin's disease and not a part of the disease. In a series of eight cases clinically diagnosed Hodgkin's

disease at The Johns Hopkins Hospital a careful histological study during life revealed the characteristic pathological histology of Hodgkin's disease. In none of the specimens studied were the histological features of tuberculosis revealed or tubercle bacilli detected. In one of the cases that came to autopsy an associated miliary tuberculosis was discovered, which was interpreted as a terminal infection.

Based upon her own studies and a review of the literature, Reed agreed with the Viennese pathologists that Hodgkin's disease was purely an inflammatory granulomatous process but entirely rejected the tubercle bacillus as the underlying cause of the disease for the following reasons:

| <i>Tuberculosis</i> | <i>Hodgkin's Disease</i> |
|---|--|
| 1 Necrosis and caseation are the rule | 1 Necrosis and caseation are rare unless secondary infection occurs |
| 2 Invades and breaks through the capsule of the gland | 2 Does not invade and break through the capsule of the gland |
| 3 Shows miliary tubercles or general inflammatory changes with typical caseation, Langhans giant cells and tubercle bacilli | 3 Shows typical non-tuberculous histology unless complicated by tuberculosis as a secondary phenomenon |

When tuberculosis occurs in Hodgkin's disease, Reed concluded, it is always a distinct pathological condition and may be present either as (a) a concomitant condition in different organs, (b) an associated condition in the same organs or tissues affected by Hodgkin's disease, or (c) a terminal condition in the course of the disease.

Thirty-one years have now elapsed since Reed's classical description of Hodgkin's disease. During these years a voluminous literature has sprung up dealing with the various phases of lymphosarcoma and Hodgkin's disease. With few exceptions, the overwhelming majority of investigators have embraced the viewpoint of the Viennese pathologists that a sharp line of demarcation exists between lymphosarcoma and Hodgkin's disease. Lymphosarcoma is regarded as a frankly neoplastic disease while Hodgkin's disease is looked upon as a purely inflammatory granulomatous process—a lymphogranuloma.

Among the first clear dissenting voices sharply disagreeing with the views of the majority were those of Benda⁶ and Chian⁷ and Yamasaki.⁸ In a small series of cases of typical Hodgkin's disease observed by them, careful morphological studies revealed invasion of the capsule of the glands and of the veins. The chief biologic characteristics which distinguish a malignant neoplasm from a benign growth, namely, invasive growth into the neighboring tissues and vascular channels, were found by them to be present not only in lymphosarcoma but also in Hodgkin's disease. The most important differential points which Kunderat had stressed between lymphosarcoma and Hodgkin's disease were thus proved to be untenable. Nor did their studies corroborate the views of Sternberg that Hodgkin's disease is merely an atypical form of tuberculosis masquerading in the guise of pseudoleukemia. The tubercle bacillus was entirely excluded as a causative

factor in the group of cases of Hodgkin's disease studied by them histologically and bacteriologically

In 1906 Gibbons⁸ of San Francisco published a careful morphological study of nine cases of classical Hodgkin's disease. These strikingly brought to view the incorrectness of Kundiat, Paltauf and Steinberg's differential criteria between lymphosarcoma and Hodgkin's disease. In Gibbons' cases the capsule of the gland was invaded, the neighboring tissues were invaded and infiltrated, the normal structure of the gland was obliterated, the mode of extension was regional and metastatic-hematogenous, the invasion of liver and spleen was definitely nodular, eight of the nine patients were adults and all of them males. In no case was tuberculosis found as an associated condition.

Gibbons was especially impressed by the invasion of blood vessels and the hematogenous mode of dissemination of the proliferating cells. Contrary to the belief which still prevails today among many eminent pathologists that Hodgkin's disease develops only in areas of preexisting lymphoid tissue by the invasion of the unknown infectious agent of the disease, Gibbons noted that the specific lesions in the viscera seem to originate in the vicinity of blood vessels. In one of the cases "in which the lung was affected, the metastases showed plainly that they were not alone developments of preexisting lymphoid tissue in the organ, but progressed as true malignant metastases by pushing the tumor structure already formed into adjacent tissues, destroying them, and occupying their places, while large nodular metastases occurred in the lower lobe removed from the invading part of the tumor and not in the vicinity of the bronchi—that is in a situation where no lymphoid tissue exists normally."

Having been thus impressed by the gross anatomic malignant characteristics of Hodgkin's disease, which fully paralleled those of lymphosarcoma, Gibbons carefully reviewed the morphological-histological reasons that have induced many pathologists then—as well as now—to declare Hodgkin's disease a non-neoplastic inflammatory granulomatous infectious disease. These reasons dogmatically given then as now are. In neoplastic growth it is only one type of cell which shows the proliferative growth, while in granulomatous proliferation many cells participate in the process. In lymphosarcoma the growth is composed entirely of atypical lymphocytes, hence it is a true neoplasm, while in Hodgkin's disease there is a polymorphous proliferation of endothelioid cells, lymphocytes, fibroblasts, eosinophiles, giant cells, polynuclear cells, plasma cells and mast cells.

Gibbons' conclusion was that morphologically also there is no fundamental distinction between Hodgkin's disease and lymphosarcoma. Histologically, he found that the pathological tissue in Hodgkin's disease is composed of a proliferation of cells of the germinal centers of the gland, the endothelium lining the sinuses, the reticulum cells of the connective tissue, capsule and blood vessels. The proliferation may go on simultaneously from the three sources or one may outstrip the others. *If it goes on with*

the same tempo in all the three tissues the morphological picture is that of classical Hodgkin's disease, if one cell type outstrips the others we have more in the foreground the sarcomatous nature of the process The correctness of this viewpoint is attested by the transition stages of affected glands in which even the staunch supporters of the inflammatory granulomatous nature of Hodgkin's disease find it difficult or impossible to differentiate it from sarcoma and have therefore suggested a Hodgkin's type of sarcoma⁹ Clinically, biologically, and morphologically Gibbons concluded, Hodgkin's disease and lymphosarcoma are not sharply demarcated diseases but merely variations of the same malignant neoplastic process, namely, lymphosarcomatosis

One year later, in 1907, Coley¹⁰ stated "My own conclusion, based upon a study of upwards of 600 cases of sarcoma, 76 originating in the lymph glands of the neck, is that Hodgkin's disease is merely a variety of sarcoma, maintaining as a rule a fairly definite clinical and pathological type, but yet, in many cases, shading off into other types that correspond most closely with the ordinary types of round cell sarcoma If the malignant nature of the disease becomes generally accepted, as I believe it undoubtedly will, it will be hard to find a better name for the disease than lymphosarcoma or lymphosarcomatosis"

In 1908 further studies by Coley¹¹ and Dietrich¹² stressed the local invasive character of Hodgkin's disease and its frequent invasion of veins, hence favoring hematogenous dissemination Nevertheless, the sharp line of demarcation between lymphosarcoma and Hodgkin's disease was stoutly maintained in the standard textbooks and monographs dealing with Hodgkin's disease, and, even in the two outstanding comprehensive studies on Hodgkin's disease by Fabian¹³ and Ziegler¹⁴ published in 1911, in spite of a wealth of evidence in favor of the close clinical, biological, and morphological relationship between Hodgkin's disease and lymphosarcoma, their fundamental difference was strongly upheld This nearly universal viewpoint was disturbed in 1911 by only one dissenting case report by the veteran pathologist Chiari,¹⁵ who recorded the autopsy findings in a case clinically and microscopically diagnosed Hodgkin's disease The findings showed compression of the esophagus, invasion of lungs and pericardium, and discrete nodules in the spleen Microscopically, the normal architecture of the lymph glands was gone The capsule was invaded, the fat and bronchi were infiltrated, and the veins and arteries were definitely invaded A search for tubercle bacilli and Fraenkel and Much¹⁶ organisms proved negative

In 1913 Oliver¹⁷ published a study of 22 cases of lymphosarcoma, 11 cases of Hodgkin's disease and 13 cases of endothelioma of lymph nodes His conclusions are Hodgkin's disease must be classed with lymphosarcoma and endothelioma of lymph glands as a neoplastic process for the following reasons

1 The similarity, and in certain cases the identity, of the histologic process

2 The early and constant invasion of the capsule and veins

3 The ultimate formation of true metastases, partly at least through the blood stream

In none of the cases of Hodgkin's disease studied by Oliver was there any histological evidence of the presence of tuberculosis or of the Fraenkel and Much organism

In 1914 it appeared as though at last the true nature of Hodgkin's disease as a mere variation of lymphosarcoma was gaining recognition among the official teachers of pathologic histology. For, that year marked the publication of "The Principles of Pathologic Histology" by Dr. Frank Mallory,¹⁸ an outstanding student of morphological histology, who classed Hodgkin's disease among the frankly neoplastic diseases as a lymphoblastoma, a mere variation of lymphosarcoma. Indeed, he overreached himself when he designated Hodgkin's disease as scirrhus lymphoblastoma, for certainly Hodgkin's disease during its early evolution has a phase as highly cellular as lymphosarcoma. On the other hand, lymphosarcoma, as stressed by Kundrat³ in his original paper on lymphosarcomatosis, presents during the course of its evolution a scirrhus stage, phase, or variety as in Hodgkin's disease.

Was it overemphasis of the late degenerative or regressive phase or stage of Hodgkin's disease and the slighting of the early highly cellular polymorphous phase of the disease which accounts for Mallory's failure to make sufficient impression upon the profession? Or, was it the apparently ultra-radical view—a view already suggested by Banti¹⁰ in 1903—which would embrace in one group Hodgkin's disease, lymphosarcoma and lymphatic leukemia—which made Mallory's classification unacceptable to the majority of pathologists who are strong adherents of static morphological histology? Whatever the explanation is, the fact remains that Mallory's views found very limited acceptance among pathologists outside the Harvard group.

In 1915 one of the early students of our problem, Dr. William B. Coley,²⁰ published a comprehensive monograph on "Primary Neoplasms of the Lymphatic Glands Including Hodgkin's Disease." His vast experience and further studies since his first publications on the disease had thoroughly impressed upon him the common nature of lymphosarcoma and Hodgkin's disease. "In one of my cases," he states, "a tumor of the axillary glands was pronounced in the original report, lymphosarcoma, and the same pathologist described it two years later as an endothelioma. Other specimens were pronounced round-celled sarcoma by one pathologist and Hodgkin's disease by another. This is common observation." The same year Bloomfield²¹ reviewed the bacteriological evidence produced by Fraenkel and Much,¹⁹ de Negri and Mieremet,²² Bunting and Yates,²³ and others pur-

porting to show that Hodgkin's disease is an infectious disease caused by diphtheroid organisms His conclusions were

- 1 Organisms can frequently be cultivated *intra vitam* from diseased as well as from apparently normal glands

- 2 There is a higher proportion of successful cultures from definitely diseased glands than from those apparently in a normal condition

- 3 None of the 29 strains isolated in the author's series of cases could be shown to be the cause of specific disease

- 4 Pleomorphic diphtheroid organisms were isolated not only in a few cases of Hodgkin's disease but also in lymphosarcoma, carcinoma, arthritis and other conditions

- 5 Injections of diphtheroid organisms into a monkey failed to produce any definite lesions

- 6 Autogenous vaccine therapy given in two cases of Hodgkin's disease and in three cases of infectious arthritis failed to produce any results

One year later, 1916, Ghon and Roman²⁴ published a comprehensive study on lymphosarcoma based upon an extensive review of the literature and a thorough histological study of 31 cases They draw a sharp distinction between Hodgkin's disease, which they consider as a lymphogranuloma, and lymphosarcomatosis, which they regard as a frankly neoplastic disease They state that clinically and gross-anatomically the two diseases cannot always be differentiated One wonders, however, how can such differentiation always be made even on the basis of histological morphology in the light of their verified observation "In lymphosarcoma we find fairly represented all the cellular elements of lymphadenoid tissue lymphoblasts, lymphocytes, macrophages, plasma cells, and even giant cells"

Perhaps even more important than this observation of the presence of polymorphism of cells in lymphosarcoma as in Hodgkin's disease was their observation of the frequent invasion of blood vessels by the lymphosarcomatous growths and their tendency to hematogenous metastases, as in Hodgkin's disease Kundrat's original claim that hematogenous metastases in lymphosarcoma are absent or very rare and that extension of the disease is from one group of lymph nodes to another or from one lymphoid area to another—a belief still widely held today by many clinicians and pathologists—was entirely disproved by Ghon and Roman's thorough and careful histological observations A detailed study of the mode of dissemination of lymphosarcoma in 27 out of their 31 cases revealed

- 1 Direct extension and metastases to regional lymph nodes in six cases

- 2 Direct extension and metastases to regional and distant lymph nodes in four cases

- 3 Lymphogenous and possibly hematogenous metastases in five cases

- 4 Local lymphogenous and hematogenous metastases in 12 cases

Two years later Warfield and Kristjanson²⁵ reported a case which on first admission to hospital gave the distinctive pathologic picture of lympho-

sarcoma Upon readmission the blood picture was that of acute lymphatic leukemia, while glands removed from the axilla just before death showed a picture indistinguishable from typical Hodgkin's disease

In 1917 Cunningham²⁶ again reviewed the status of diphtheroids with special reference to Hodgkin's disease and produced proof that the diphtheroid organism in a series of cases of Hodgkin's disease was a mere laboratory contamination and could not be obtained in typical cases of Hodgkin's disease when careful bacteriological methods were used to prevent contamination

In 1921 Mueller²⁷ published a study of 16 cases of Hodgkin's disease In two of the cases the disease exhibited "a change in the histological structure from typical lymphosarcoma to round-celled sarcoma or vice versa In one of the two cases the disease exhibited malignant neoplastic properties with invasion of lungs, aortic wall, and spinal canal" From a morphologic-histological point of view," Mueller concluded, "the opinion seems justified that lymphosarcoma and round-celled sarcoma of the lymph-nodes are only different expressions of the same process"

In 1925 another one of Kundrat's differential diagnostic dogmas between lymphosarcoma and Hodgkin's disease was completely disproved by Liu²⁸ of Pekin, China In a study of 12 cases of lymphosarcoma of the small intestine from the pathological department of The Johns Hopkins Hospital, Baltimore, Liu found stenosis of the gut in 10 of the cases Kundrat's original observation of the presence of dilatation in lymphosarcomatous tumors of hollow viscera—which led him to the hasty generalization that invasion of hollow viscera by lymphosarcoma causes dilatation of lumen, never constriction—was thus proved untenable, and once again the danger of generalizing from a comparatively small number of cases was emphasized

One of the most instructive cases of Hodgkin's disease showing its close relationship, if not identity, with lymphosarcoma was published by McCartney²⁹ in 1928 A woman of 52 developed progressive loss of weight, pallor and dyspnea, followed one year later by enlargement of the cervical lymph glands A biopsy of one of these glands was reported small round-celled sarcoma Several months later, in 1927, nodes removed from the neck and axilla were reported lymphatic leukemia The patient died in March 1928 Autopsy revealed invasion of lymph glands, skin, lungs, liver, and kidneys by nodular growths

Microscopic examination showed "In one lymph node four distinct histologic types are present In some areas one sees the typical picture of Hodgkin's disease with Dorothy Reed type of cell In other areas the appearance is that of lymphatic leukemia In many places there are numerous spaces lined by an endothelial type of cell, giving an appearance simulating closely but not quite duplicating that of primary endothelioma of lymph nodes Finally certain areas show a large type of cell with marked

evidence of active growth, with numerous mitotic figures and a small amount of reticulum, an appearance commonly called lymphosarcoma. Scattered through the node are microscopic areas of necrosis and marked fibrosis." The involved visceral organs showed similar histological pictures.

The same year, 1928, Coley³⁰ reported a new series of 58 cases of lymphosarcoma and 39 cases of Hodgkin's disease. He reiterates "For many years I have held that these two conditions, which are usually regarded as quite different and distinct, are actually quite closely allied etiologically, and bear such a close resemblance to one another that in some instances it is impossible to differentiate them either clinically or histologically."

Further recent studies entirely in agreement with the view that Hodgkin's disease and lymphosarcoma are merely variations of the same malignant neoplastic process were recorded by Letulle, Tremolières and Moussour,³¹ Callender,³² Warthin,³³ Levin,³⁴ Wellbrock and Lougherty,³⁵ and others.

My own observations and studies during the past 13 years, based upon more than 100 cases of Hodgkin's disease and lymphosarcoma, are entirely in agreement with the viewpoint that biologically, clinically, and morphologically they are merely variations of the same disease. To justify this viewpoint, in the course of our study, abundant detailed evidence will be submitted, of which the following two case reports will serve as introductory illustrative examples.

CASE I

Mrs. V. G., aged 54, was admitted to the Montefiore Hospital on September 13, 1929, complaining of pain in the right shoulder, a lump in the right axilla, progressive weakness, and loss of weight. Duration of symptoms, seven months.

In February 1929, without any apparent predisposing or exciting causes, she developed pain in the right shoulder. A few weeks later she discovered a painless lump in the right axilla. Prompt medical consultation resulted in a diagnosis of tumor of the right axillary lymph glands and operation was advised. A resection of the tumor was done on April 28, 1929, by a prominent New York surgeon, who found the mass "composed of glands of various sizes. Some were quite hard and felt like carcinoma, others were much softer and had the appearance of sarcoma." The pathologist's report was typical Hodgkin's disease.

One week after the operation the patient developed an acute chest condition which was diagnosed as pneumonia. The respiratory symptoms subsided within a few weeks but her general health showed progressive deterioration. She became very asthenic and partly bed-ridden.

On admission to the Montefiore Hospital on September 13, 1929, she looked pale and emaciated. The mouth showed a few remaining carious teeth and no other abnormality. There were many stony hard and matted together lymph nodes in both cervical regions. There was a scar in the right axilla and no recurrence of any tumor mass. The lungs showed slight dullness at apices and bases. The heart showed no abnormalities. The liver was palpable about 5 cm. below the costal margin. The spleen and kidneys were not palpable. There was a median ventral hernia. The rectal and vaginal examinations were negative.

Radiographic examination of the chest on September 20, 1929, revealed normal lungs and mediastinum and moderate left ventricular enlargement.

Blood examination showed hemoglobin 90 per cent, white blood cells 10,000, polynuclear leukocytes 78 per cent, lymphocytes 20 per cent, eosinophiles 2 per cent. The blood Wassermann was negative. Urinalysis was essentially negative.

Course under Roentgen Therapy Following deep roentgen display to the cervical lymph nodes the masses decreased in size but the patient's general condition gradually grew worse. Reexamination on January 12, 1930, found her complaining of profound weakness and a completely bed-ridden state, dryness of the throat, cough and expectoration, profuse night sweats, pain in the right upper posterior chest, pain in both arms and in the lumbosacral spine. She looked paler than on admission. The following superficial lymph glands were found to be enlarged: right pre-auricular, left cervical, left axillary, right epitrochlear, and left inguinal. The right breast was enlarged and markedly edematous. The skin over it had a typical pig-skin appearance. The lungs and heart did not show any gross abnormality. The abdomen failed to reveal any tumor masses. The spleen was not palpable. The liver was felt 5 cm below the costal margin. The lower extremities showed slight edema.

On February 23, 1930, a hard immovable, circumscribed, tender mass measuring 5 by 5 by 3 cm was noted over the upper sternal region and contiguous chest wall. The mass felt bony-hard in consistency and seemed to be fused with the ribs and sternum. At this time a radiographic examination of the chest revealed an area of consolidation in the right lower lobe. It also showed a slight thickening of the periosteum along the anterior surface of the first portion of the sternum. There was a partial collapse of the body of the seventh dorsal vertebra to about half its size.

The predominant clinical symptoms were toxic and respiratory. She ran a remittent febrile course with temperatures to 103°. A blood count, done on March 18, 1930, showed 3,600,000 red blood cells, 75 per cent hemoglobin and 8,600 white blood cells. The polynuclear leukocytes were 86 per cent, lymphocytes 8 per cent, monos 4 per cent, eosinophiles 1 per cent, and basophiles 1 per cent.

Cautious deep roentgen-ray therapy was applied to the chest lesions with little effect upon the course and development of her illness. She steadily went down hill and died from toxemia and respiratory embarrassment on September 27, 1930.

Necropsy revealed (1) Hodgkin's disease involving the cervical, mediastinal, periaortic, retroperitoneal, mesenteric, peri-pancreatic and iliac lymph nodes, the thyroid, right breast, both lungs, right bronchial tree, spleen, pancreas, stomach, jejunum, cervix, vagina, bladder and vertebral bone marrow.

2 Bilateral hydronephrosis

3 Chronic purulent cholecystitis, cholangitis and cholelithiasis with stones in the hepatic duct and in the papilla of Vater

4 Ulceration of the neck of the gall-bladder

5 Extreme fatty metamorphosis of the liver

Detailed Study of the Hodgkin's Lesions *Skin and Breast* Above the right breast and extending into the axilla is a 16 cm old scar. The right breast is about twice the size of the left. The skin is thickened and wrinkled and shows two fairly punched-out ulcerations. There is considerable edema of the right arm. Over the skin of the chest the infiltration is rather hemorrhagic in character. On section, the right breast shows a plum-sized mass of exceptional firmness, homogenous, grayish in appearance, rather gristly in texture from which strands of similar tissue are seen to extend crab-like through the adipose tissue and into the underlying tissue. The pectoral muscles are almost completely absorbed and the fascia above the thorax is markedly infiltrated by this firm, gray tissue. Microscopically the lesion presents the typical picture of Hodgkin's disease. The wall of one of the veins and its vasa vasorum show invasion (figures 1 and 2).

Bones Four contiguous lumbar vertebrae examined reveal diffuse replacement of red marrow by a yellowish, homogeneous, firm tissue.

Neck Organs The cervical lymph nodes are enlarged and on section show a similar firm homogeneous tissue. There is a small, circumscribed, whitish-gray nodule in the right lobe of the thyroid. Microscopically the nodule, apparently a lymph node,



FIG 1 (Case I) Diffuse invasion and infiltration of Hodgkin's disease in the wall of a breast vein. Suspicion of invasion of vasa vasorum



FIG 2 Invasion of vasa vasorum by Hodgkin's reticulum and giant cells

entirely replaced by Hodgkin's tissue, is seen to infiltrate the capsule and invade the thyroid (figure 3)

Trachea and Bronchi The mucosa of the trachea is slightly injected. Beginning just above the bifurcation there is a marked alteration of the mucosa of the bronchus

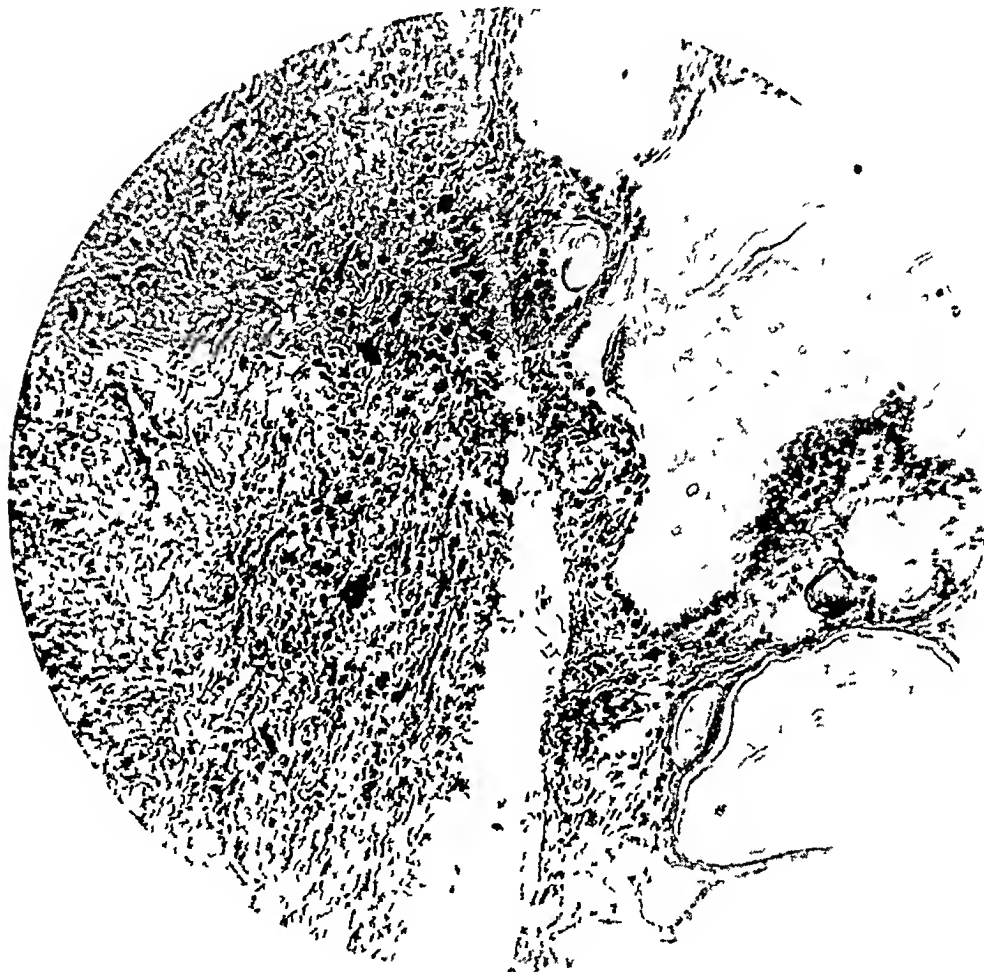


FIG 3 (Case I) Invasion of thyroid by Hodgkin's disease

which is considerably thickened, very irregular and apparently replaced by a similar very firm, homogeneous, grayish tissue. The change extends into the smaller ramifications of the bronchi to both upper and lower lobes. Tracheo-bronchial lymph nodes are enlarged and very firm. On section they are markedly degenerated but are definitely invaded by a similar tissue.

Lungs The right lung feels heavy and there is a peculiar sensation on palpation due to scattered areas of almost wooden consistency throughout the entire lung. Posteriorly and over the anterior surface of the upper lobe there is complete obliteration of the pleural cavity. The remaining surface of the lung has a mottled emphysematous and congested appearance. The lung is very pale. Occasionally one sees beneath the pleura a circumscribed, very small raised nodule composed of a

homogeneous grayish tissue On section there is an astounding picture The upper lobe is almost entirely replaced by exceedingly firm, raised, pigmented, homogeneous, grayish tissue which is very sharply defined from the pale and somewhat edematous normal lung These nodules, varying in size from an orange to a plum, constitute about three-quarters of the upper lobe The lower lobe is fairly well aerated, pale in color Scattered throughout are small circumscribed nodules of a similar, very firm, grayish, slightly pigmented tissue The parietal pericardium is firmly adherent to the mesial surface of the right lung

Microscopical Examination Many of the alveoli are filled with fibrinous material and serum In the interstitial tissue and extending into the alveoli are typical Hodgkin's tissue, Dorothy Reed giant cells, occasional lymphocytes and areas of fibrosis and necrosis

The mediastinal lymph nodes are markedly enlarged Microscopical examination shows typical Hodgkin's

Heart Extreme fibrosis Marked calcification of the coronaries

Abdomen The peritoneal cavity is free from fluid The mesentery is atrophic and contains numerous enlarged and discrete lymph nodes which on section contain a very firm grayish tissue from which no juice can be scraped Some of these nodules show a considerable amount of pseudo-mucin

Spleen Slightly enlarged Weighs 210 gm Measures 12 by 8 by 5 cm The capsule is smooth, slightly wrinkled and reddish-gray in appearance Notches are well preserved On section the pulp has a fleshy, rather homogeneous appearance, and yields little on scraping Trabeculations are quite marked Near one blood vessel is an almost wedge-shaped area made up of very firm grayish tissue At the lower pole there is replacement of the pulp over an area the size of a cherry by a very firm, glistening, grayish tissue Microscopic examination reveals large areas of necrosis and hemorrhage with areas of fibrotic Hodgkin's tissue The uninvolved portion of the spleen shows atrophy of pulp tissue with very small follicles

Stomach and Jejunum On the anterior wall of the stomach in the fundus, are two circumscribed, dime-sized ulcerations of the mucosa with fairly thickened walls Numerous enlarged nodes are present along the attachment of the mesentery to the peritoneal surfaces of the small and large intestines In the mid-portion of the jejunum there is an ulceration of the mucosa about 4 by 1.5 cm whose long diameter is perpendicular to the direction of the intestines The edges of the ulceration are very firm and are raised On the serosal surface are several small collections of firm, grayish tissue which are in relation with a very large node in the mesentery near by Microscopically the mucosa and submucosa are infiltrated with typical Hodgkin's tissue

Gall-Bladder and Liver Free from any neoplastic tissue on gross and microscopical examination

Pancreas A small area at the head of the pancreas containing compressed but relatively normal tissue is all that remains of the normal pancreas The remainder, including the body and tail and a portion of the head, is replaced by a very firm, homogeneous, rather gristly tissue in which are a few yellowish areas (figure 4) This infiltration of the pancreas causes a threefold increase in the size of the involved portion Numerous lymph nodes in this region at the head of the pancreas and along the greater and lesser curvature of the stomach are replaced by similar tissue

Suprarenals Normal in size and shape and free from tumor tissue

Kidneys Free from tumor Both pelves and ureters are slightly dilated The terminal thirds of both ureters are in close relation to and compressed by a chain of enlarged lymph nodes extending from the bifurcation of the aorta along the iliacs to the femoral region

Iliac Vessels Are firmly ensheathed in a large group of lymph nodes

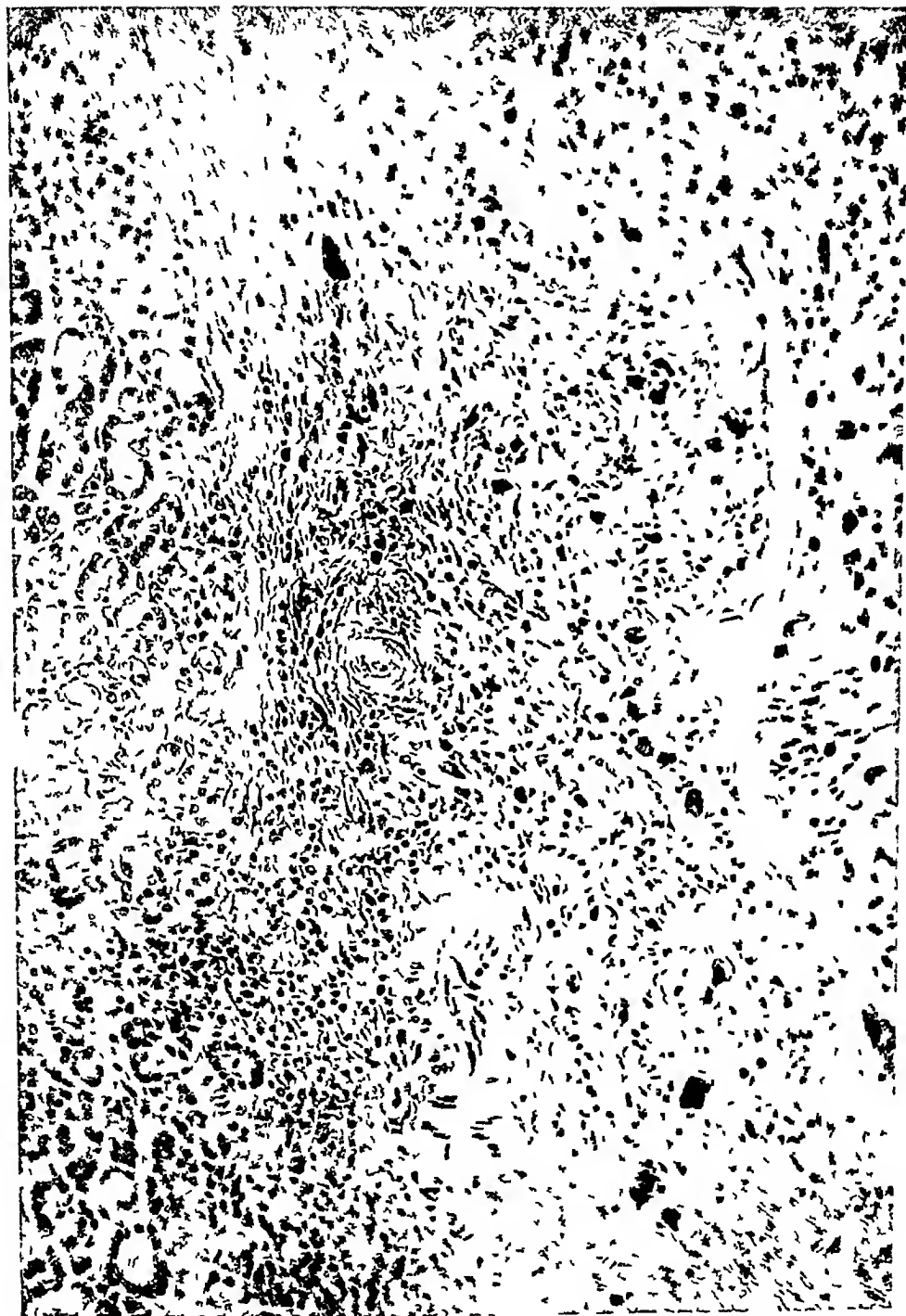


FIG 4 (Case I) Invasion of pancreas by Hodgkin's disease

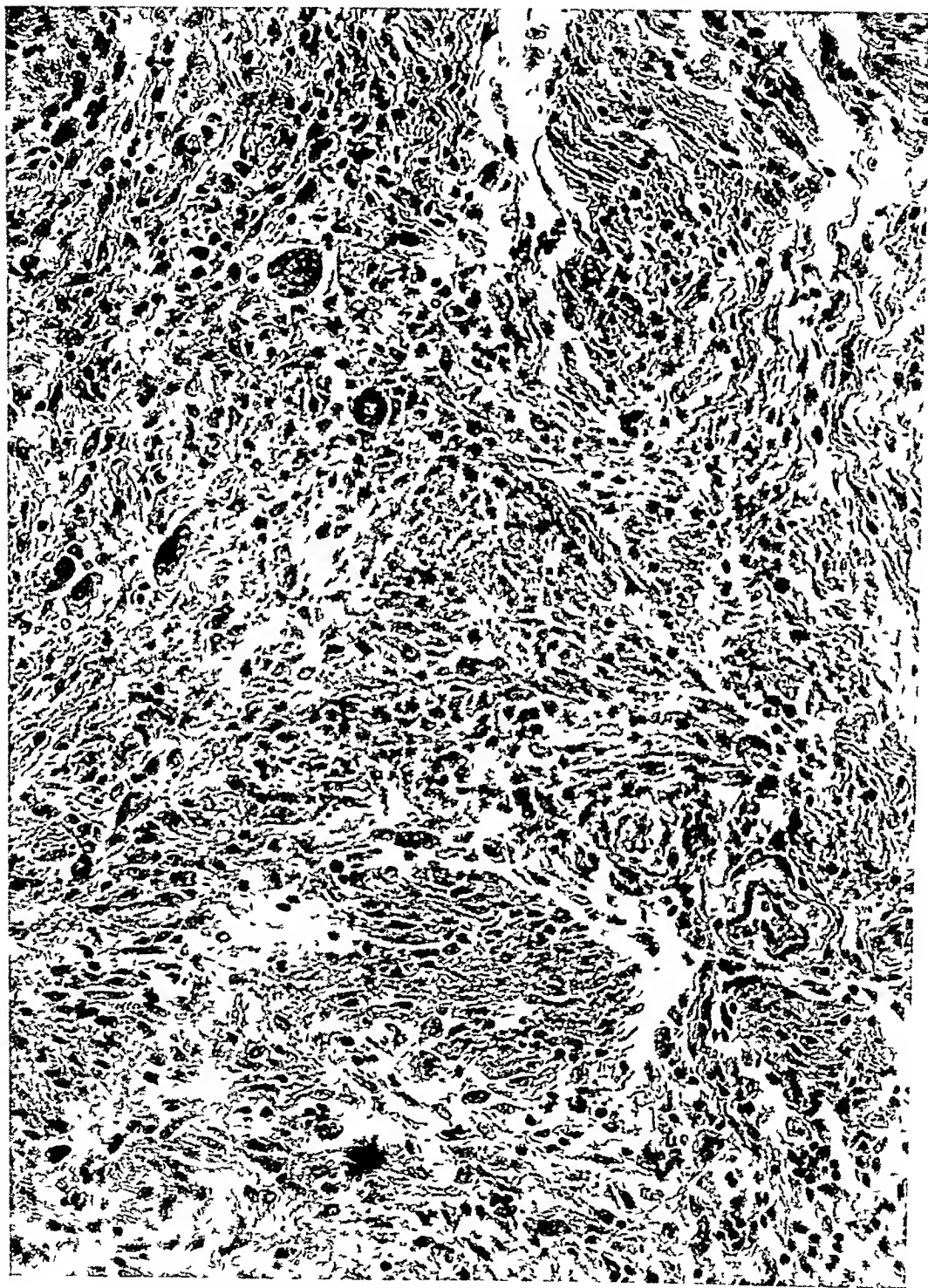


FIG 5 (Case I) Invasion of uterus by Hodgkin's disease

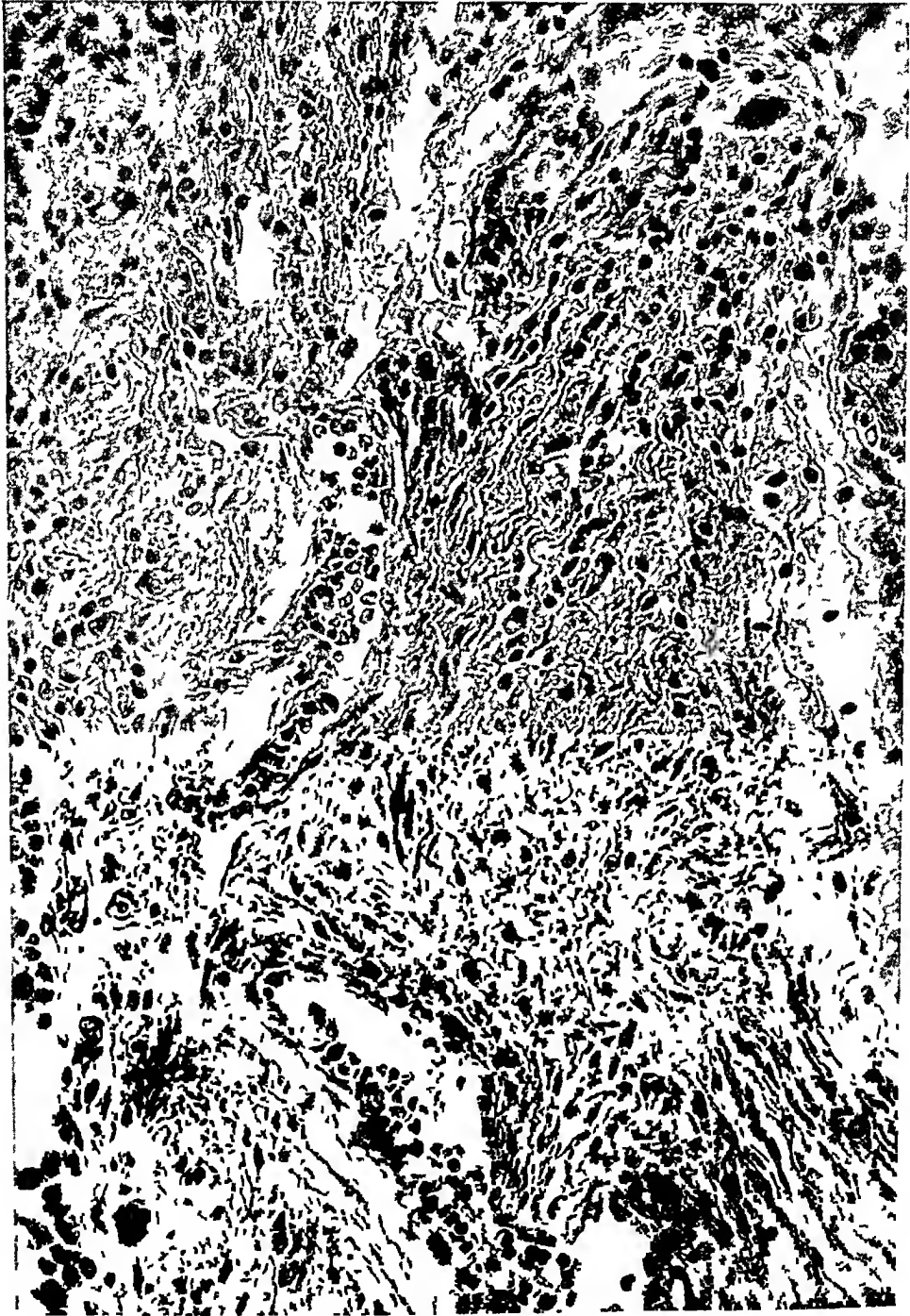


Fig 6 (Case I) Invasion of bladder by Hodgkin's disease

Ovaries Fallopian tubes and rectum are free from tumor

Uterus The upper right fundal portion of the uterus is replaced by a homogeneous yellowish-gray appearing tissue which is confined entirely to the muscular coat (figure 5) The cervix is markedly enlarged and on section contains similar tissue

Vagina The upper portion of the vagina shows numerous serpiginous ulcerations, and submucosal thickenings caused by growth of similar very firm tissue

Bladder Grossly no evidence of tumor growth Microscopically the wall of the bladder is infiltrated by Hodgkin's tissue (figure 6)

CASE II

Mrs M H, aged 61, journalist, was admitted to the Hospital on February 21, 1924

Chief Complaints Pain in upper abdomen, left lower posterior chest, left lumbar and lower sacral regions, paraplegia, parasthesia of lower extremities, tumor mass over hip, marked weakness and loss in weight Duration of symptoms, 14 months

Present Illness On January 1, 1923, without any apparent predisposing or exciting causes, while stooping forward to lace her shoes she was seized with a violent twisting pain in the left upper abdomen, recurring several times during the day and lasting each time a few minutes The next day she consulted a local physician who diagnosed visceroptosis and advised the wearing of an abdominal belt The belt was promptly donned and gradual subsidence of pain in the abdomen followed Shortly thereafter she experienced a dull aching pain in the left lower lateral chest She immediately consulted another local physician who discovered an enlarged spleen and had her blood examined Internal medication was prescribed with gradual relief of the pain in the chest In February she began to have drawing and twisting deep-seated pain in the upper mid-abdomen sharply localized and non-radiating The pain was constant and severe but was not accompanied by any other local or constitutional symptoms In May she consulted another local physician who diagnosed myalgia and myositis and prescribed a liniment and internal medication In June she began to have very severe pain in the lower part of the spine aggravated on motion She was forced to spend most of the time in bed to obtain partial relief from pain

In July her daughter, while giving her a rub-down with alcohol for the sore lower spine, discovered a mass the size of a hen's egg over the right hip The mass was neither painful nor tender and according to the patient's observation had apparently not undergone any change in size until admission to Montefiore Hospital some six months later

In August she was taken to a large hospital in New York where her spine was radiographed and pronounced negative The presence of the lump over the right hip apparently elicited no comment or attention and she was discharged with a diagnosis of lumbago

Gradually the pain in the lower spine increased in severity, disability became more marked and she became almost completely bed-ridden

In November she consulted a gynecologist for cystocele which she herself had noticed a year before and which she now suspected as the possible cause of her severe and disabling backache The presence of cystocele was confirmed and at her own request a pessary was inserted The gynecologist, however, did not feel quite convinced that the cystocele was the sole cause of the underlying complaints and advised orthopedic consultation This was promptly agreed to She was examined by an experienced orthopedist who ordered a brace for supposed spondylitis Unfortunately, however, neither brace nor pessary produced any relief from the severe backache and within a few days after their application she developed prickling and numbness in the soles of both feet gradually extending upward to the hypogastrium and associated with weakness of both lower extremities

In December the pessary was removed but the paraplegia became more pronounced and she was unable to sit up in bed

In January 1924, she was admitted to a hospital in New York where her case was diagnosed as postero-lateral sclerosis of the lower lumbar cord possibly due to tumor. The presence of a tumor over the right hip and invasion of the lungs by neoplasm were also noted but their exact interrelationship was not understood. The patient was given a series of intramuscular injections without the slightest benefit and on February 21, 1924, nearly 14 months after the onset of her first complaints, she was admitted to the neurological service of Dr. Philip S. Goodhart at the Montefiore Hospital.

Examination revealed an old pale-looking and emaciated woman presenting no cachexia, dyspnea or cyanosis. The skull and scalp were negative. The teeth were almost all gone, only a few badly carious ones remained. The tongue was heavily coated and tremulous and the left half was atrophic. The tonsils were small and buried behind the pillars. The pharynx was free from any neoplastic disease. The neck showed no enlargement of lymph nodes. The thyroid gland was not palpable.

Chest and Lungs Diminished vocal fremitus and dullness from the top of the right scapula to the base. A few slightly enlarged lymph nodes were palpable in the left axilla, none in the right.

Heart Negative

Abdomen Distended, tympanitic. On deep palpation a diffuse doughy mass can be felt along the midline. The liver is palpable 4 cm. below the costal margin, the surface is smooth, the edge sharp. The upper level of liver dullness extends to the fifth intercostal space. The spleen is palpable 1 cm. below the costal margin. The iliac, inguinal and femoral lymph nodes are greatly enlarged, discrete, non-tender, varying in size from $\frac{1}{2}$ to 2 to 3 cm. Over the left gluteal region a mass the size of a hen's egg, soft, non-tender and freely movable, is present.

Rectal and Vaginal Examination Negative

Neurological examination reveals involvement of the twelfth cranial nerve evidenced by slight fibrillary tremor affecting the whole tongue and atrophy of its left half. There is definite paraplegia. A sensory belt of hyperesthesia begins about two inches above and ends about two inches below the umbilicus. Below this belt there is hypesthesia. Very little motion is possible in the lower extremities. The patient can just lift her knee off the bed but cannot maintain it in that position. There is a bilateral Babinski and markedly exaggerated knee jerks.

Laboratory Data Radiographic examination of the chest shows a dense homogeneous shadow extending from the right apex to the base. Blood examination moderate secondary anemia. White blood cells 11,200, polynuclears 74 per cent, small lymphocytes 9 per cent, large lymphocytes 6 per cent, mononuclears 6 per cent, mast cells 2 per cent, eosinophiles 2 per cent. Urine analysis practically negative. Biopsy of lymph node shows large reticulum cell lymphosarcoma.

Course under Roentgen Therapy Following deep roentgen therapy to the lower spine and chest there was slight recession in symptoms. The further clinical course of the disease was mainly characterized by further generalization of the neoplastic process, progressive wasting, persistent toxemia and terminal pneumonia superimposed upon the neoplastic lung involvement.

Necropsy revealed generalized lymphosarcoma with involvement of mediastinal, retroperitoneal, iliac and inguinal lymph glands, thyroid, sternum, pleura, lungs, heart, peritoneum, small intestines, adrenals, liver and kidney.

Detailed Autopsy Report The body is that of an elderly, slenderly built, markedly emaciated female, 150 cm. long.

Scalp, brain, pituitary and pineal negative.

Eyes, ears and nose negative.

Mouth Mucous membranes pale

Teeth Many missing, remainder well kept

Tongue Negative

Tonsils Small, pitted, scarred

Larynx and Trachea Normal

Neck Negative except for a few shotty glands on both sides along the lateral borders of the sterno-mastoid

Thyroid Both lobes slightly larger than average, the right hard though smooth. There is an elongated nodule of apparently normal thyroid on the right side of the midline separate and distinct from the right thyroid lobe which measures 1.5 by 0.5 by 0.3 cm. On section, the greater portion of the right lobe with the exception of the upper pole is replaced by smooth grayish white tissue in the center of which is a small area of calcification. The left lobe contains an ill defined nodule 1.5 cm in diameter in its upper pole, the remainder of the lobe is apparently normal and colloid containing. Microscopic examination shows isolation and replacement of thyroid follicles by tumor throughout.

Parathyroids Normal

Upper Extremities Negative

Chest Breasts atrophic. Slightly to the left of the midline in the region of the third and fourth ribs is a bulgy, firm tumor mass about 7 cm in diameter, over which the skin is freely movable. The mass is seen to infiltrate the elevated intercostal muscles and the medial portions of the pectoral muscles. The removal of the sternum and costal cartilages is accomplished with difficulty because of extensive tumor involvement of the mediastinum and the anterior surface of the pericardial sac.

Pericardial Sac There is a wide layer of tumor tissue externally which binds the pericardial sac to the medial surface of both lungs. On opening the pericardial sac, both the visceral and parietal surfaces are covered with a shaggy fibrinous layer and in the parietal pericardium are numerous flattened grayish white tumor nodules, discrete and confluent, measuring up to 2 cm in diameter and 5 mm thick.

Heart Weighs approximately 200 gm. The entire visceral pericardium is covered with shaggy fibrinous exudate. On section the heart muscle is decidedly brown and injected. No abnormalities are found in the endocardium or valves. *Microscopic* Muscle fibers are thinned out, the vessels slightly thickened. An organizing fibrinous layer is found on the epicardial surface. In the edematous epicardium is a small tumor area.

Right Pleural Cavity Is completely obliterated in its upper two-thirds, in its lower third it is filled with a hemorrhagic fluid containing large fibrin masses. The parietal and visceral pleura all over is markedly thickened and in the region of the diaphragm measures 5 mm.

Right Lung The two upper lobes are air-containing throughout. The lower lobe is markedly collapsed, atelectatic. On section, both upper lobes are markedly edematous and slightly congested, the lower lobe collapsed and dry. The tumor tissue in the visceral pleura measures up to 7 mm in thickness along the diaphragmatic and visceral borders. The bronchi are slightly dilated. The larger arteries are slightly but distinctly thickened throughout. The root glands are enlarged, grayish white, firm.

Left Pleural Cavity Contains about 700 c.c. of clear straw colored fluid and a few dense fibrous adhesions at the apex of the upper lobe and over the posterior surfaces of both lobes. There are numerous small tumor nodules on the parietal pleura.

Left Lung Both lobes are fairly well collapsed. A few fibrous tags are present on the parietal surfaces. There is a healed scarred area at the apex of the upper lobe. Scattered throughout the visceral pleura of both lobes are flattened nodules.

up to 1 cm in diameter and 3 mm thick. On section, both lobes are moderately congested and edematous. The bronchi are dilated, the vessels normal. The root glands are markedly enlarged and at the hilum they surround the larger bronchi and appear underneath the mucous membrane. *Microscopic* Extensive replacement and diffuse tumor infiltration of lungs with areas of necrosis and fibrosis.

Abdomen Spleen small and free from tumor.

Liver Weight 880 gm. Small, soft. Capsule thin. On the inferior surface are numerous small nodules up to 1 cm in diameter, 3 mm thick. On section, tissue greasy brown, lobulations fairly regular, numerous tumor nodules up to 5 mm in diameter are seen and a single large nodule 2 cm in diameter. Microscopic examination reveals invasion of veins by tumor cells.

Esophagus and Stomach Negative for tumor.

Duodenum There is an elevated nodule 7 mm in diameter and 2 mm thick, immediately anterior to the ampulla. The remainder of the duodenum is negative.

Jejunum and Ileum At irregular intervals are numerous, slightly flattened, nodular, grayish white and injected tumor nodules in the mucous membrane, measuring from 3 to 7 mm in diameter and 2 to 4 mm thick. These nodules are numerous in the jejunum and do not infiltrate the muscle layers.

Pancreas Free from tumor.

Appendix Coiled up in a mass of adhesions though on section the lumen is patent throughout.

Cecum Except for a nodule of tumor tissue on its peritoneal surface in the region of the adhesions described, no abnormalities are seen. Microscopically tumor tissue infiltrates the muscle layers and the peritoneal coverings of the cecum and appendix.

Colon No abnormalities.

Suprarenals The right suprarenal weighs 5.5 gm and is of average size and consistency. On section, the cortical tissue is narrow and fatty, and the medulla is softened. The left weighs approximately the same and is for the most part adherent to the tumor tissue on its posterior surface. On section, the cortical tissue is fatty, the medulla is prominent, and there is a small tumor nodule 5 mm in diameter in the medulla.

Kidneys Each weighs 110 gm and is of average size and consistency.

Right Capsule slightly diffusely adherent and in places firmly adherent to large tumor nodules. The nodules appear on the surface as slightly elevated, grayish white nodular areas up to 2 cm in diameter and slightly umbilicated. The remainder of the surface shows marked superficial pitting. On section, there is slight congestion throughout. The tumor nodules are seen to replace large portions of the cortex and pyramids, but in places the architecture is still retained. The striations are regular and prominent. At the hilum the tumor tissue is seen surrounding but not occluding the larger vessels. Pelvis and ureter negative.

Left Contains small tumor nodules but is otherwise similar to the right. The large arteries are markedly thickened.

Ovaries, tubes, vagina, and bladder are free from tumor.

Microscopic The tumor consists of fairly uniformly sized, small polygonal cells with irregular nuclei, the latter are in instances pale staining, and occasionally multilobulated. There are a moderate number of mitotic figures, rarely a syncytial giant cell. In places the cells are small and round, resembling lymphocytes.

COMMENT

A parallel study of the above two cases reveals the following very instructive facts:

- 1 Both were females past middle life.
- 2 In neither case was there any predisposing or exciting cause to explain the etiology of the disease.

3 In neither case was tuberculosis found on postmortem examination

4 Invasion of the capsule of lymph glands and invasion and infiltration of neighboring tissues occurred in the Hodgkin's case no less than in the lymphosarcomatous case

5 Obliteration of the structure of glands occurred just as freely in the one as in the other

6 Extension in the Hodgkin's as well as in the lymphosarcoma case was regionally invasive and metastatic through lymph and blood channels. Invasion of veins and hematogenous mode of systemic dissemination were demonstrated in both

7 Infiltration of hollow viscera did not differ from metastatic invasion in epithelial cancerous growths

8 In both cases bone was invaded

9 The lesions in both were predominantly nodular or diffusely infiltrative in different tissues and organs

10 Both diseases, although widely generalized, were, on gross and microscopic study limited to about the same number of organs and tissues, as follows

Lymphosarcoma Case

Lymph glands, thyroid, bone, pleura, lungs, heart, peritoneum, small intestine, cecum, appendix, adrenals, liver, kidney

Hodgkin's Case

Lymph glands, thyroid, skin, bone, breast, lungs, bronchi, spleen, pancreas, stomach, jejunum, uterus, vagina, bladder

11 Necrosis and hemorrhage occurred in lesions of both types. Though fibrosis was more marked in the case of Hodgkin's disease the clinical course of the disease was not materially altered thereby

12 Both ran a mild remittent fever

13 Eosinophilia in the blood was absent in both

14 Toxemia and cachexia were more marked in the case of lymphosarcoma than in that of Hodgkin's disease

15 Both died from toxemia and pulmonary involvement without any marked compression of mediastinal structures

16 The clinical duration of life was 24 months in the lymphosarcoma case as against only 20 months in the Hodgkin's case

Biologically, therefore, Hodgkin's disease varies in no fundamental characteristic from lymphosarcoma. Whatever variations it may present at times are merely variations that one would expect to find in any disease affecting different individuals under different constitutional and environmental conditions

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THE ENCEPHALITIS EPIDEMIC IN ST. LOUIS¹

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DURING the summer and autumn of 1933, 1097 cases of epidemic encephalitis were reported in St Louis and in St Louis County¹ Study of the disease has revealed that it differs in many important respects from the encephalitis lethargica of von Economo and that it is not definitely identifiable with the Japanese Encephalitis B Although it has previously attracted little attention, it may not be entirely new in this country In 1932 cases of a similar condition were seen in the small city of Paris, Illinois, where in a population of 9000, 27 cases were reported^{2,3}

Due to a most effective organization of the Health Department of St Louis and to admirable cooperation between local and Federal agencies, unusual opportunities were afforded for study of the entire epidemic⁴ Over 90 per cent of the reported cases were treated in hospitals where clinical records are readily available The correlation of these data has been placed in the hands of a committee which is representative of the many agencies involved in the work and which will soon publish a comprehensive monograph Although the report of the committee will furnish an authoritative and detailed analysis of the clinical and laboratory observations, it does not seem inappropriate that a brief outline should be presented before the College of Physicians at this time, more particularly since outbreaks of a similar character and of greater or less severity may possibly occur in other communities during next July, August and September

The summer of 1933 in St Louis was unusually hot and dry June was the hottest ever recorded After heavy spring rains there was a prolonged drought and in June, July and August the rainfall was the lowest in the history of the city Conditions of drainage were favorable to the breeding of extraordinary numbers of mosquitoes

It is now known that a case of encephalitis was seen as early as July 7 and that several isolated cases were observed in St Louis County during that month A state of epidemic became dramatically apparent on August 8, when the City Isolation Hospital received from the county 16 cases of an unusual type of encephalitis Others rapidly followed Since such an experience was entirely new in this country it is not surprising that much confusion in diagnosis occurred Because of the severe headaches and high fever, the not infrequent bradycardia and leukopenia, typhoid was often suspected It is interesting that requests for Widal tests from the health department were 100 per cent higher than in a similar period of the previous year In some cases the chill of onset led to a suspicion of malaria Signs of meningeal irritation with increased mononuclear cell count in the spinal

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fluid suggested even to experts the probability of tuberculous meningitis. When from pathological studies encephalitis was demonstrated, it was naturally assumed that the disease was encephalitis lethargica in an atypical form and that it would be followed by the usual distressing residuals. The well justified fear of encephalitis lethargica and its consequences no doubt contributed to the widespread attention given to an epidemic which, although serious, involved only about one in one thousand of the population in a limited area.¹

CLINICAL FEATURES

Clinical study of the disease has revealed a striking similarity in the symptoms of individual patients with modifications referable in large part to the intensity of infection, the localization of lesions, to age and previous physical and mental constitution^{5, 6, 7}. A typical case of maximum severity may be cited.

A white woman of 53 left her home on the morning of September 6 apparently in good health. While working she was suddenly seized with severe headache and vomiting. She soon became delirious and on the following day was somnolent. On September 9 when she was brought to Isolation Hospital she was stuporous, her temperature was 105°, and her pulse rate was 154. The conjunctivae were injected. There was moderate injection of the naso-pharynx, a marked rigidity of the neck, a gross tremor of the lips and tongue, absent abdominal reflexes, exaggerated deep reflexes, positive bilateral Kernig and extensor response to plantar stroking of both great toes. The white blood cell count was 10,200. The spinal fluid was under increased pressure, gave a positive Pandy test and contained 82.0 mg per cent of sugar. There were 200 cells per cu mm with 90 per cent of lymphocytes. The urine contained albumin, red blood cells, white blood cells and casts. Two days later she died with a temperature of 107.4°.

A milder case and one more representative of the disease as it occurred in children was seen in a colored boy of six. On August 27 he was seized with headache and vomiting followed by drowsiness and pain on bending his neck. Two days later he entered the Isolation Hospital, where examination revealed a temperature of 103°, an injected pharynx, a tremor of the tongue, slight rigidity of the neck, and diminished deep reflexes. There were no pathological toe signs and the abdominal reflexes were present. The white blood cell count was 9400. The urine was normal. The spinal fluid was under moderately increased pressure and contained 130 cells, 91 per cent of which were lymphocytes. The Pandy test was negative. Sugar, as determined by the Benedict method, was present in the fluid. His temperature fell by lysis and in three days was normal. He was discharged on September 21 without symptoms or signs of disease.

An extremely mild case observed by Dr. T. C. Hempelmann may also be cited. This was a 19 year old girl who, although she had had headache, photophobia, a sensation of fever for a period of six days, had not been

confined to bed. At the time of entrance to the hospital she was found to have 107 cells in her spinal fluid. Five days later and on the eleventh day of her disease she felt entirely well and wished to go home.

The purposes of this paper permit no extensive analysis of symptoms. In about half the cases the onset of the disease was sudden, often with a chill or with vomiting, occasionally with convulsions, which were seen in adults as well as in children. In other patients there seemed to be a period of invasion for three or four days with fever, headache, general pains, photophobia and conjunctivitis and slight rigidity of the back and neck. At the end of this prodromal period a sharp rise in temperature was common and the subsequent course was similar to the cases of more abrupt onset.

Although several patients revealed no fever during the period of observation, the usual temperature at the height of the disease was 103 to 104°, in occasional cases rising to 106°. The pulse was usually proportional to the temperature but bradycardia was not infrequent and tachycardia was observed in some of the more severe cases.

Headache, stiff neck, and a positive Kernig sign were relatively constant symptoms. Although diplopia or blurring of vision was noted in many, strabismus, ptosis, and facial weakness were relatively uncommon, occurred early and were usually transient. The abdominal reflexes, which varied greatly with the stage of the disease, were often absent during acute severe illness. The deep reflexes varied too greatly to be of diagnostic importance. Pathological toe signs were not infrequently encountered.

Coarse tremors of the hands and arms often increased by intention and gross tremors of the tongue were seen in many cases. The speech was uncertain and tremulous. Although many patients appeared somnolent or even stuporous, they could usually be aroused sufficiently to answer questions. In a few cases delirium and sleeplessness were prominent features.

The white blood cell count usually ranged from 10,000 to 14,000 with extremes from 2800 to 36,000. During the acute stage the Schilling differential revealed a moderate infectious picture but was not sufficiently characteristic to serve as an aid in diagnosis or prognosis.

The spinal fluid during the acute stage was often under increased pressure. In the majority of instances 100 to 300 cells were recorded but this was subject to considerable variation and in one fluid 1100 cells were found. Lymphocytes usually predominated, although at times polynuclear cells constituted from 30 to 50 per cent of the total. It is important to note that in some cases the fluid withdrawn on the first spinal puncture was normal while a second puncture a day or two later revealed the characteristic increase in cell count. Of diagnostic significance were the sugar determinations which by the Shaffer-Hartmann method varied from 20 to 146 mg per cent, in the great majority of cases being well above the range seen in tuberculous meningitis.

The urine, often normal, showed in many instances albumin and casts,

but in amounts not greater than those encountered in other acute infections. In a few cases changes indicative of extensive renal damage were found.

A relatively short course was characteristic of the disease. The fever usually remained high from three to five days, and then gradually fell, reaching normal in 7 to 10 days after the onset. A critical drop in temperature, however, was not uncommon. Somnolence or stupor persisted during the febrile course. The cell count in the spinal fluid often remained high after all subjective symptoms had disappeared and in some cases was still elevated three weeks after the onset when the patient was discharged from the hospital.

PROGNOSIS

Among 1059 cases there were 221 deaths, a mortality of almost exactly 20 per cent¹. The prognosis was not clearly dependent upon the degree of meningeal involvement, the height of the initial temperature or the number of cells in the spinal fluid. The age of the afflicted individual was of the greatest importance, the mortality being less than 5 per cent in patients under 40 and approximately 50 per cent in those over 60. Most of the deaths were attributable in part to complications, by far the most

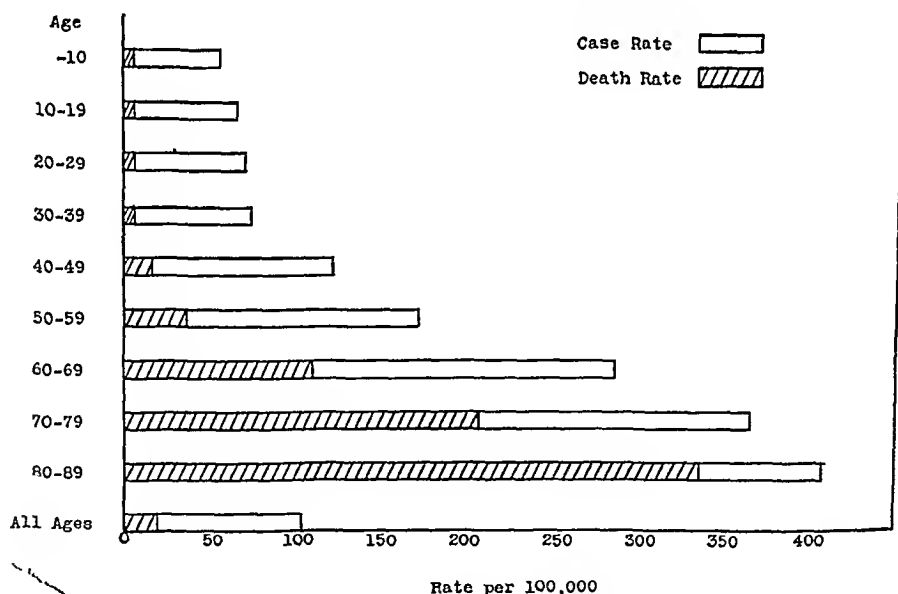


FIG 1 Incidence and Mortality Rate at Various Ages
(Data from the St. Louis Health Department¹)

frequent of which was pneumonia. Previously existing nephritis, hypertension and arteriosclerosis seemed to play an important rôle. Several patients who had not been previously recognized as nephritics died in uremia. Not more than 10 per cent of the deaths could be attributed to uncomplicated encephalitis.

Although serious residual manifestations were uncommon, some degree of disability was apparent in many patients at the time they were discharged from the hospital. In December, approximately three months after the subsidence of the epidemic, an examination was made of 375 of the 447 surviving patients in the City of St. Louis. Of these, 133 revealed no residual symptoms. One patient had remained in a state of delirium. Another was subject to convulsions. Paralyzes or localized weakness of muscles were seen in 21. Personality changes such as excitability, melancholy or sullenness were found in 45. Forgetfulness or confusion, usually slight, was not uncommon. Tremor of some degree was still apparent in 72 patients. The most usual complaints were of headache and general pains. Sleeplessness, weakness and fatigue were also frequently mentioned. While this survey has shown that complete recovery occurred after three months in less than half the cases, it is fair to say that most of the changes were slight and that few were disabling. Especially encouraging is the fact that no new symptoms of encephalitis had developed and that there was no single instance of progression of the disease.

PATHOLOGY

The pathological lesions, although sufficiently distinctive to establish a diagnosis of encephalitis, did not serve to differentiate sharply the cases of the St. Louis epidemic from those of encephalitis lethargica. Possibly

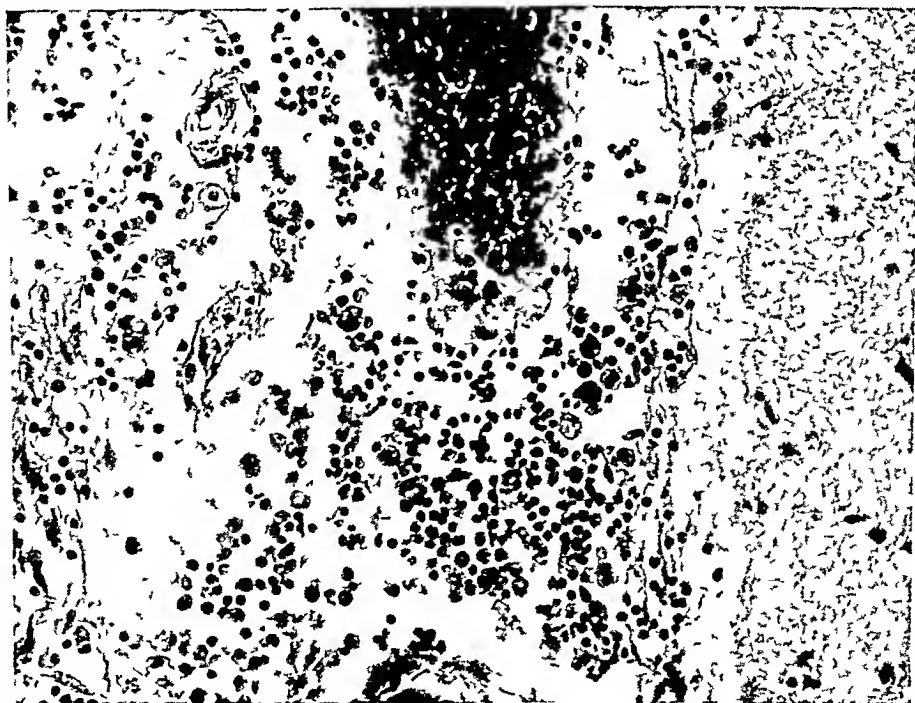


FIG 2 Section of brain and meninges showing extensive infiltration of the meninges by cells, most of which are lymphocytes

the most notable difference was the widespread distribution of the lesions in the St Louis form of the disease. Characteristic changes⁸ were found in the meninges and throughout the brain, in the cortex, in the white substance of the hemispheres as well as in the pons and basal ganglia. They were also seen in the spinal cord. To the naked eye the most striking change was the congestion and dilatation of meningeal and intracerebral blood vessels. Capillaries were distended sufficiently to give to many parts of the brain a pinkish discoloration. The diagnosis usually depended upon (1) the intense congestion of blood vessels, (2) the infiltration of round cells about blood vessels, the so-called perivascular cuffing, and (3) the nerve cell degeneration which consisted of swelling, eccentricity of the nucleus and chromatolysis and which was usually accompanied by focal accumulation of round cells. It is of clinical interest that the nuclei of the cranial nerves were not especially involved.

In many of the fatal cases there was a hemorrhagic and edematous type of pneumonia similar to that observed in individuals dying early in the course of acute epidemic influenza. The kidneys were frequently swollen and intensely congested, with cloudy swelling of the cortex and extensive degenerative changes in the convoluted tubules. In several cases intranuclear inclusions, first noted by Dr Margaret Smith, were demonstrated in the tubular epithelium.

ETIOLOGY

The disease has been reproduced by intracerebral inoculation both in monkeys and in mice. While only about 40 per cent of monkeys are susceptible even to large inoculations, white mice may be uniformly infected by material in one-millionth dilution. Brain virus instilled intranasally in mice also has produced the disease. The lesions produced in experimental animals are consistently those observed in human cases. The investigations of Muckenfuss, Armstrong and McCordock,⁹ and of Webster and Fite¹⁰ have failed to demonstrate bacteria either in the blood or spinal fluid of patients or in the brains of experimentally infected animals. Webster has shown that the virus is filterable. Thus far 11 strains of virus transmissible to mice have been obtained in four different laboratories.

It has also been shown that the sera of patients recovered from the St Louis type of encephalitis possess neutralizing antibodies.¹⁰ Diluted virus suspended and incubated with convalescent serum does not kill mice, whereas the same virus mixed with normal serum kills regularly. To a lesser degree antibodies are present in the sera of some of the nurses and doctors who were exposed to the disease but were never ill. Neutralizing properties against the virus have also been shown in the sera of five patients who had recovered from encephalitis in Paris, Illinois, and of two patients from New York who had suffered from encephalitis thought to resemble the St Louis type.¹¹

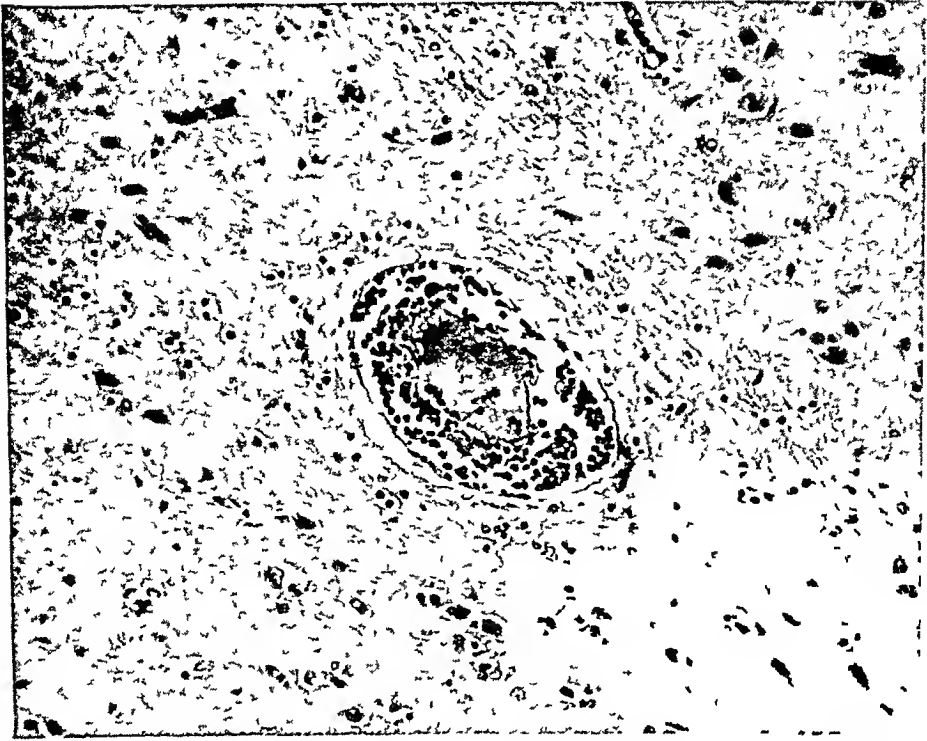


FIG 3 Section of brain showing perivascular infiltration (cuffing) with lymphocytes

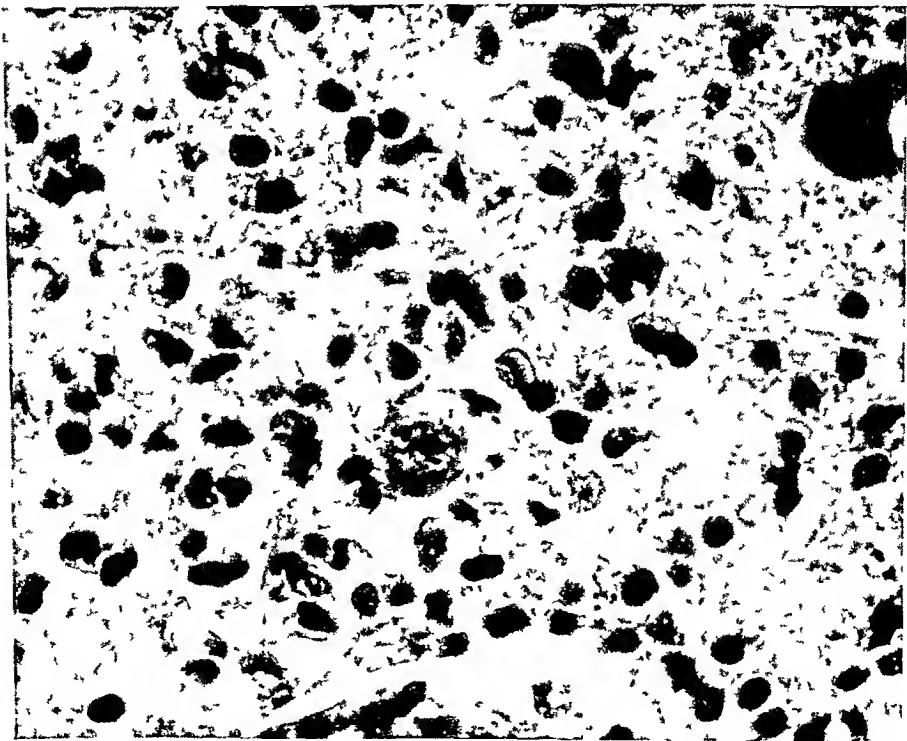


FIG 4 Higher power showing cellular infiltration about nerve cells. At the upper right there is a degenerative nerve cell in which no nucleus is visible

The contention¹² that lethargic encephalitis and the St Louis type of encephalitis are one and the same disease is fraught with many difficulties. The sudden onset, the relatively short course, the prominence and severity of meningeal symptoms, the low incidence of cranial nerve palsies and particularly the rarity of serious residual and progressive lesions are features difficult to reconcile with the clinical picture of encephalitis lethargica. Furthermore, neutralization tests have indicated that those who are suffering from lethargic encephalitis have no neutralization antibodies for the St Louis virus¹¹.

On the other hand, the clinical manifestations of the Japanese Encephalitis B are almost identical with the St Louis disease. In both there is an acute onset, high fever, meningeal as well as cerebral involvement, a short rapid course with recovery or death in a week or 10 days. In both there is a relatively low incidence of sequelae. The Japanese disease has occurred in the late summer and early fall and has carried a high mortality in older individuals. In the light of this striking similarity of clinical features, it is surprising that the sera of Japanese patients apparently do not neutralize the St Louis virus¹³.

SUMMARY

The encephalitis which occurred in St Louis in 1933 was an acute disease of relatively short duration which so far has shown little tendency to serious sequelae. Both its incidence and its mortality were greater in older people. It was caused by a filterable virus to which both monkeys and white mice are susceptible. The sera of patients who have recovered from the disease contain neutralizing antibodies. Both clinically and immunologically the St Louis epidemic differs from encephalitis lethargica. Although in its epidemiological and clinical manifestations it closely resembles the Japanese Encephalitis B, immunological reactions have indicated that the two diseases are not identical. At present it appears that the St Louis form of encephalitis has previously escaped general attention and that it is not definitely identifiable with any known condition. The circumstances of the epidemic indicate that it may appear in other communities and presumably in the summer and autumn.

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CHANGES IN THE S-T SEGMENT OF THE ELECTROCARDIOGRAM IN ACUTE RHEUMATIC FEVER *

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PROLONGATION of the a-v conduction time and alterations of rhythm are the electrocardiographic changes best known to occur in the presence of acute rheumatic fever. A review of the rather scattered literature, together with our own case reports, indicates, however, that S-T (R-T) changes are not uncommon. They deserve much attention because they indicate objectively alterations of the heart musculature.

CASE I

The patient was a male, aged 25 years, who was seen first in the hospital February 14, 1933. He gave a history of rheumatic fever at seven years and of chorea at nine years of age. Six weeks previous to examination he had a recurrence of rheumatic infection followed by loss of weight, dyspnea and a left-sided paralysis of short duration. Examination revealed dyspnea, clubbing of the fingers, pallor, enlargement of the spleen and liver, one skin nodule and some glandular enlargement. There were pain and stiffness in several joints. The apex impulse of the heart had its maximum intensity in the anterior axillary line in the sixth intercostal space. A loud diastolic murmur was heard best in the third and fourth left intercostal spaces, and to the right of the sternum was heard a systolic murmur transmitted into the vessels of the neck. There was no evidence of pericarditis. The heart rate was 102 per minute and regular. The pulse was characteristic of the Corrigan type. The blood pressure was 130 systolic and 80 diastolic. The blood count showed 3,860,000 red blood cells, 10 grams of hemoglobin and 16,400 leukocytes. The Wassermann was negative. Roentgen-ray examination showed marked enlargement of the left ventricle and slight enlargement of the left auricle. There were increased pulsations of the left heart contour and aorta, and complete absence of signs of congestive lung failure.

The patient received salicylates and later a vaccine. He improved subjectively and objectively. Six weeks after admission, his red cell count had risen to 4,570,000, his hemoglobin to 13.5 grams and his white blood cells had decreased to 11,100. The pulse rate had dropped to 70. The heart findings remained unchanged. The blood pressure was 150 systolic and 20 diastolic. The patient eventually recovered from his acute rheumatic attack and was discharged from the hospital.

A series of electrocardiograms was taken during the course of this patient's illness. They showed interesting variations in the S-T segment and the T-wave, these variations being dependent apparently upon the stage of activity of the rheumatic infection.

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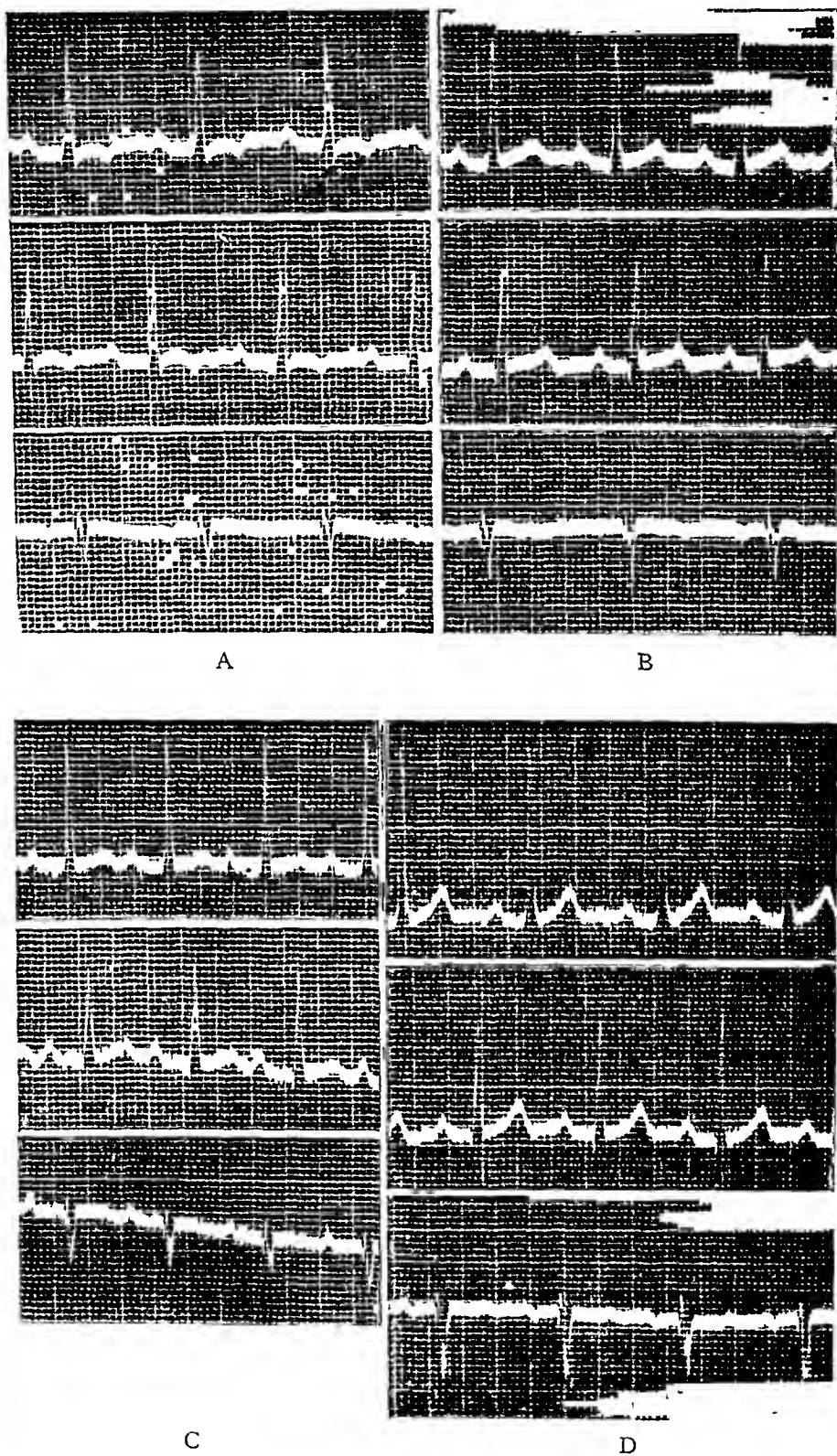


FIG 1 Case I

The first was taken February 14, 1933 (figure 1a) In addition to the prolonged P-R interval seen frequently in acute infections of the rheumatic type, changes are seen in the S-T (or R-T) segment and in the T-wave. These changes consist of low origin of the R-T interval in Lead I, convex upward bowing of the R-T interval, Leads I and II, late cove shape T-wave inversion, Leads I and II, and isoelectricity of T₃. The second tracing was taken March 6, 1933 (figure 1b) In Leads I and II the R-T segment takes its origin from the descending limb of R before it reaches the isoelectric line and immediately slants upward to form the T-wave. In other words, there is no isoelectric R-T segment, the T-wave apparently springing directly from the descending portion of R. The third tracing was taken two weeks later (figure 1c) The R-T segment in Lead I, and to a less extent in Lead II, has a higher origin than normal. The descending limb of R barely reaches the isoelectric line. The last tracing (figure 1d), taken two months later, shows the T-wave to be of higher amplitude. There is still no period of R-T isoelectricity, the upstroke of T originating still a little above the isoelectric line on the downstroke of R.

CASE II

The patient was a mulatto boy of 16 years, admitted to the hospital April 7, 1933, complaining of pain in his chest and abdomen. This pain was of several days' duration and had been accompanied by fever. At the time of admission the pain was of maximum severity over the precordium. His temperature was 104.6°, pulse 112, and respirations 24 on admission. The past medical history was negative except for the usual childhood diseases. No rheumatic history of any kind could be elicited.

Examination showed a pale colored boy, not dyspneic and apparently not in pain. The tongue was coated, the cervical glands were palpable and tender. No petechiae were found on either skin or mucous membranes. On the day of admission there was thought to be some impaired resonance over the left chest, and in fact, roentgen-ray examination showed some evidence of an early bronchopneumonia. These signs disappeared, however, both clinically and by roentgen-examination within a few days. The apex beat of the heart was 7 cm. outside the midsternum in the fifth interspace. There was a gallop rhythm at the apex, and over a very limited area in the third left intercostal space a systolic murmur could be heard. The rest of the physical examination was negative.

On the day following admission a very pronounced friction rub was heard over the precordium. This diminished in intensity after the first day but could be heard faintly for several weeks. The temperature came down very rapidly but there continued to be a slight afternoon rise for about two and a half weeks. Premature beats were present at times and occasionally a systolic apical murmur could be heard. Neither of these findings was constant. At no time was there any joint involvement. The patient's convalescence was for the most part uneventful and he was discharged June 25, 1933 in good condition.

His treatment was symptomatic and aimed principally at the correction of his anemia. His blood count varied from 62 per cent hemoglobin, 3,500,000 red blood cells and 16,000 white blood cells on admission, to 88 per cent hemoglobin, 4,600,000 red blood cells and 8,700 white blood cells. Other laboratory examinations gave the following results: Wassermann and Kahn, negative, blood cultures, negative, stool examination, negative, sedimentation rate one month after admission was

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| 45 minutes | 25 per cent |
| 1 hour | 36 per cent |

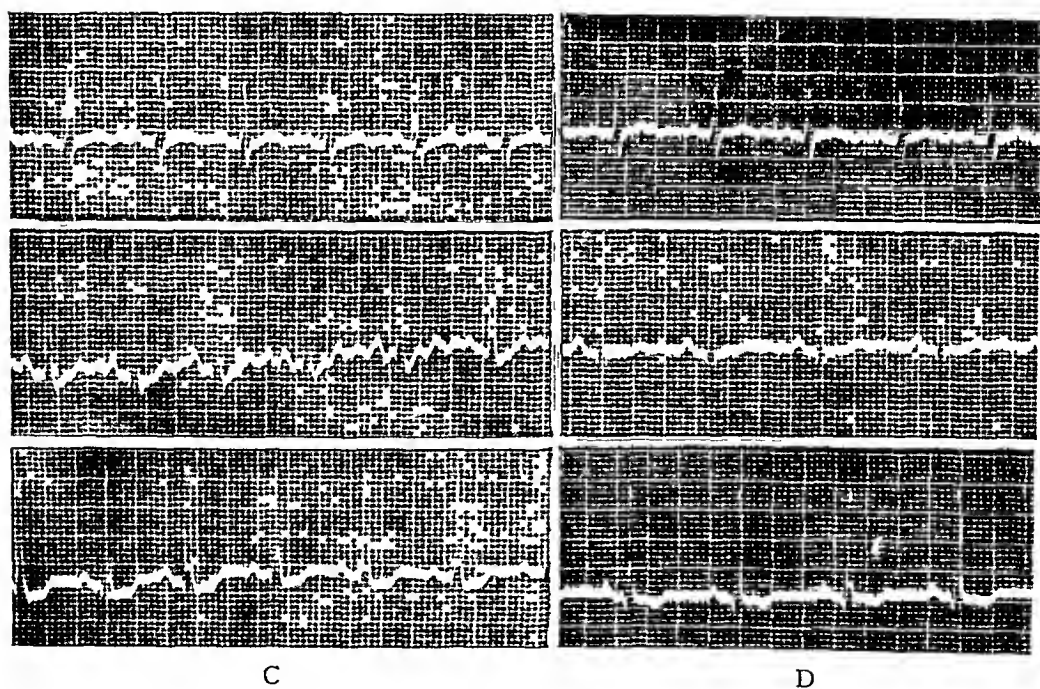
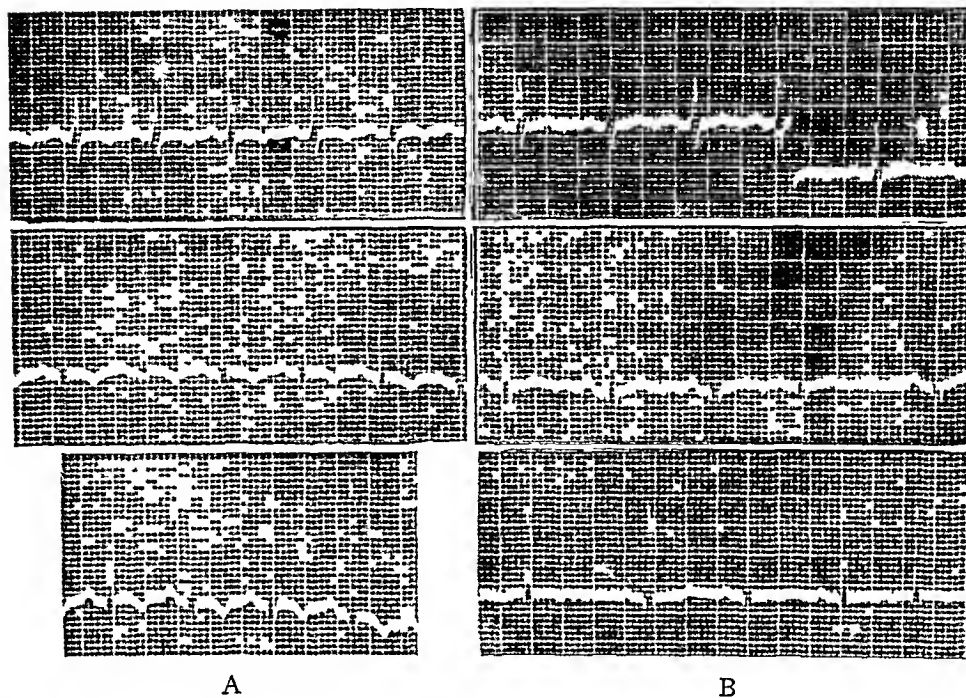


FIG 2 Case II

The test was repeated just before discharge. The results were

| | |
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| 45 minutes | 4 per cent |
| 1 hour | 5 per cent |

The basal metabolic rate was plus 6 per cent. Urine examinations showed albumin and a few granular and hyaline casts at the time of admission. On discharge the urine was entirely negative. Fluoroscopic (orthodiagraphic) examination showed the cardiothoracic ratio to be 13:21 cm.

The first electrocardiogram (figure 2a) was taken April 25, 1933. It shows T-wave inversion in all three leads. The second tracing (figure 2b), taken two weeks later, shows low voltage of the T-waves in Leads I and II and isoelectricity in Lead III. Three weeks later a third tracing (figure 2c) shows an upward directed T_1 and T_2 and inverted T_3 . All the T-waves originated below the basal line, and in the second and third leads there is a deep R-T depression. Three weeks later the fourth tracing (figure 2d) shows still an upward directed but low voltage T-wave in Leads I and II and there is much less R-T depression than was seen in the earlier picture. The last tracing (figure 3) was taken about one month later.

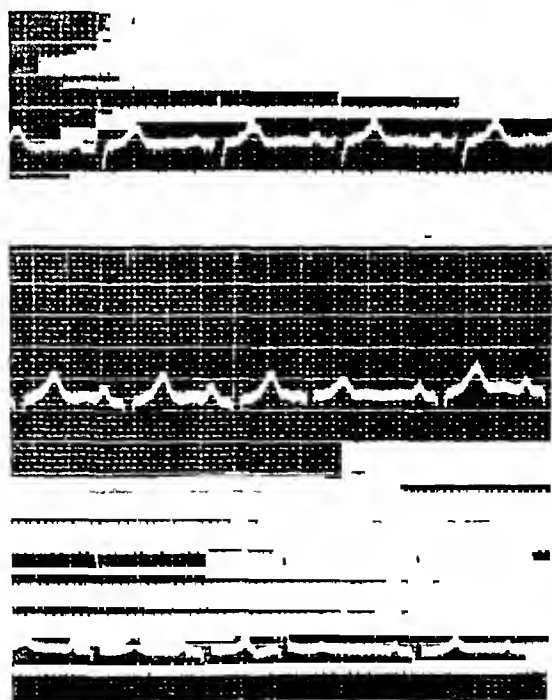


FIG. 3. Case II

This is essentially normal except for auricular premature beats and for the fact that the R-T segment in Leads I and II arises directly from the downstroke of R without a normal isoelectric period.

CASE III

The patient was a male, aged 48 years. He was admitted to the hospital May 17, 1933, with the chief complaint of generalized joint pains and sore throat. The patient had been sick at home for three months before admission. His past history

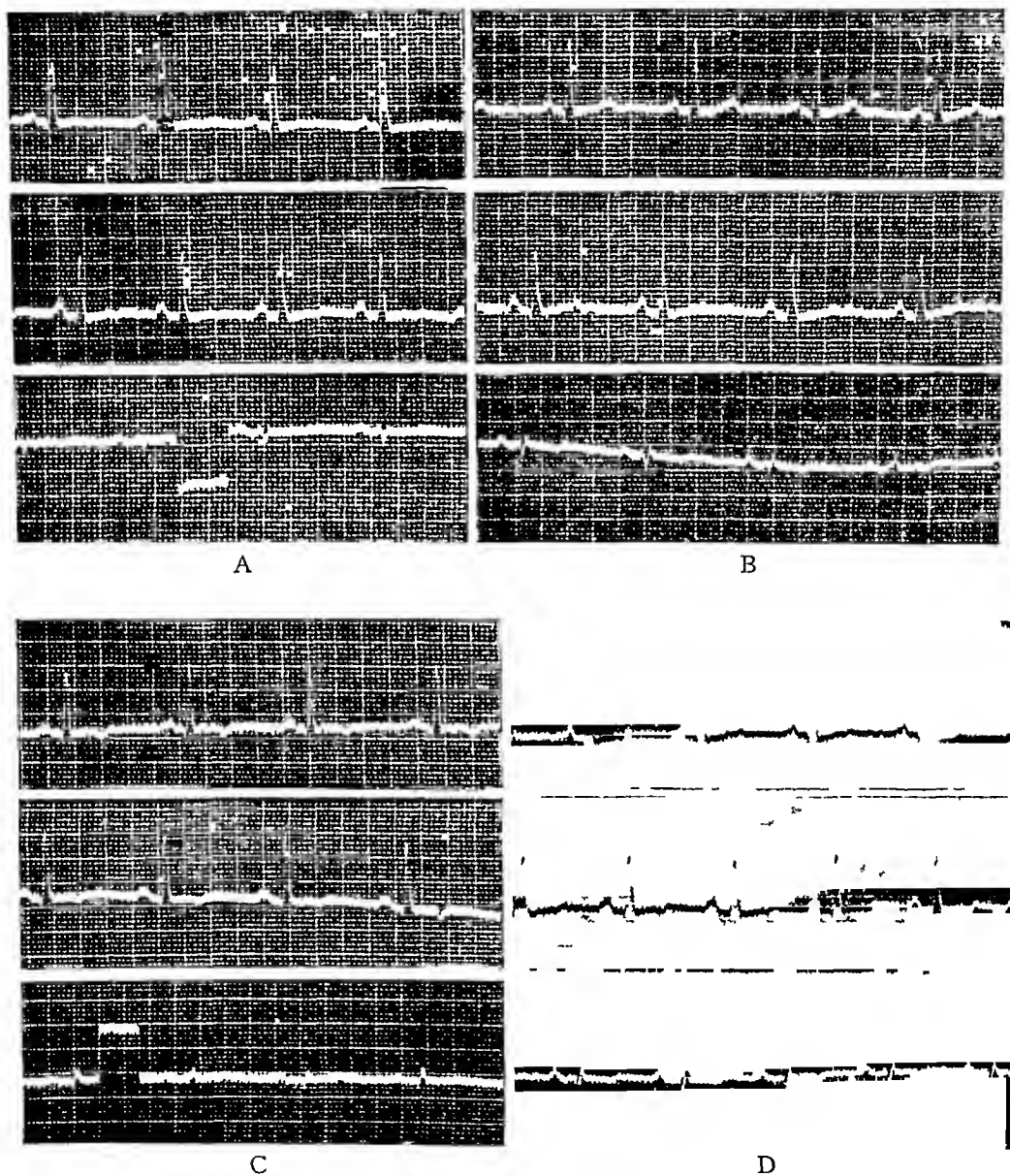


FIG 4 Case III

was negative for rheumatism but he had had scarlet fever and rather frequent sore throats in childhood. He had never had symptoms of cardiovascular disease.

On admission he was having joint pains and dyspnea. His teeth were in poor condition and his tonsils diseased. The lungs were clear. The apex beat of the heart was just outside the midclavicular line in the fifth interspace. The heart rate was 112, regular, and there was some accentuation of the second aortic sound. There

was a systolic murmur at the apex and base. The abdomen was negative. The joints of his fingers, left knee, left wrist, left elbow and shoulder were tender, swollen and hot, and there was thought to be effusion in the left knee joint. The temperature on admission was 101°.

On the day following admission, a to-and-fro friction rub was heard at the apex by one observer. This had disappeared 24 hours later and did not recur. The temperature came down to normal within about a week and the pains responded satisfactorily to salicylates. There was, however, an occasional afternoon rise of temperature of about one degree. On June 20, 1933, there was a more marked elevation for several days accompanied by the return of joint pains to a mild degree. Both fever and pain subsided after the patient was put back to bed for several days. Another rise of temperature occurred after tonsillectomy but was not in excess of what would be normally expected. There was an occasional fleeting return of joint pain, the most persistent being in one shoulder. This was effectively relieved by physiotherapy. The systolic murmur at the apex became more distinct as time went on but there was no other valvular involvement noted at any time. On admission the patient's blood count showed 73 per cent hemoglobin, 4,020,000 red blood cells and 16,250 white blood cells. One month later the count was 80 per cent hemoglobin, 4,130,000 red blood cells and 10,000 white blood cells. The urine was practically negative at all times. Sedimentation time a month after admission was

| | |
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| 45 minutes | 9 per cent |
| 1 hour | 13 per cent |

This was repeated a month later and gave practically the same results. Roentgen-ray examination showed the cardiothoracic ratio to be 17/32.5.

Electrocardiographic studies were made at intervals. The first tracings (figure 4a) were taken May 25, 1933, eight days after admission. They show a flattened T_1 , slightly inverted T_2 and an isoelectric T_3 . Three weeks later (figure 4b) the tracings show T_1 and T_2 to be upright. This was considered an improvement on the earlier ones, but on June 23, eleven days later (figure 4c) there was a distinct inversion of T_1 and T_2 . It is interesting to note that this corresponded in time to the patient's secondary rise in temperature and return of joint pain. The fourth tracing (figure 4d), taken July 16, 1933, shows a return of T-waves to isoelectricity but with a tendency for the R-T segment in Lead I to originate below the basal line on the downward limb of the R-wave.

DISCUSSION

The study of these three cases shows that in each of them the electrocardiogram has undergone changes during the course of an acute rheumatic infection. We have interested ourselves in only those changes which appear in the S-T or R-T segment or in the T-wave itself. The first case showed, during the acute infectious stage, T-wave inversion suggestive of coronary disease. This inversion showed constant improvement as the rheumatic infection cleared up, the T-wave assuming a definite upward direction. It must be noted, however, that even in the last tracing, which was taken more than two months after recovery, the T-wave arises abruptly from the downward limb of the R-wave and that there is a consequent lack of isoelectric

R-T interval The second case presents similar characteristics In the beginning there is a stage of sharp T-wave inversion, but within a period of a week or so, the T's become first isoelectric and eventually upright, although they remain of low voltage However, even in the latest tracing, in which the T-waves are upright and of satisfactory height, there is still alteration of the R-T segment The third case showed rapid improvement after the initial examination, the T-waves becoming upright and practically normal in contour in the second tracing The third tracing, however, shows definite inversion in the two first leads The patient had a reactivation of his infection at this time With his eventual complete recovery, there was still isoelectricity of the T-waves Since the R-T segment need not be absolutely flat in the electrocardiogram of normal individuals and since we have not available electrocardiographic tracings of the patients before the onset of the disease, it does not seem possible to ascribe to this finding a definite pathological significance Pardee¹ believes that rarely these alterations may be permanent, due to fibrotic changes in the myocardium, or that they may be prolonged beyond the acute manifestations of the infection, indicating possibly a continuing low grade activity A series of three cases is, of course, too small to enable one to draw conclusions regarding the frequency of these changes in rheumatic infection They afford, however, evidence confirmatory of the reports of those observers who, in the past few years, have emphasized electrocardiographic abnormalities in rheumatic infections other than the better known conduction and rhythm alterations In 1924, Cohn and Swift² reported studies on a series of 37 rheumatic patients, a number of whom showed similar R-T or S-T alterations, and they noted the similarity which some of these variations had to the type of T-wave found in recent coronary occlusion They suggested at that time that this finding indicated disturbed muscular function such as might be caused by a transient Aschoff body Bain and Hamilton³ emphasized the importance of the electrocardiogram as a means of diagnosing myocardial involvement in the course of rheumatic infections They analyzed tracings from 50 rheumatic children and found inversion of T-waves in one or more leads in eight cases, and depression of the S-T interval followed by a small T deflection in three cases They likened this finding to a "digitalis T" occurring, of course, in the absence of digitalis Rothschild, Sacks and Libman⁴ express the belief that whereas the type of change in the electrocardiogram under discussion is not pathognomonic for acute rheumatic fever, it does occur oftener in this condition than in any other single pathological state Reid and Kenway⁵ had a rather high percentage of abnormal findings in their series of 26 cases Of these, 11 showed S-T changes, and they were impressed also by the absence of S-T or R-T isoelectric periods These observers believe that there is no correlation between the duration of joint symptoms and the duration of electrocardiographic changes, and they emphasize, as do other workers, the importance of the electrocardiogram in the early diagnosis of rheumatic myocarditis McMillan

and Cook⁶ found that in 48 cases studied, 10 showed slight changes in the R-T segment and 11 showed a negative T-wave. Poite and Pardee⁷ reported on three cases with rheumatic pericarditis showing upward S-T convexity like that of a coronary thrombosis or narrowing. One of these cases at post mortem showed the left coronary artery to be thickened with an irregular subintimal proliferation. Whereas there was pericarditis present in these cases, the opinion is expressed that the abnormality in the tracings was due to inflammatory myocardial reaction, and that similar variations would appear in the absence of pericarditis.

The frequency with which pericarditis appears in the course of an acute rheumatic attack suggests the possibility that this condition in itself might be responsible for T-wave and R-T variations. Master⁸ states that the so-called coronary type of T-wave may appear in patients with rheumatic pericarditis, and furthermore that occasionally pericarditis alone may produce a flat T-wave. He cites the example of tuberculous pericarditis and cancer of the pericardium where the underlying musculature is but little involved. Cowan,⁹ however, in 1904, in a discussion of the pathological findings in the heart in acute disease, states the belief that pericarditis is a frequently unsuspected accompaniment of acute disease, and that the muscle in the vicinity of an inflamed pericardium is always degenerated. He says "As a result of pericarditis, changes may occur in the adjacent connective tissue leading to an increase in its amount, or to its degeneration, both of which necessarily cause a further defect in muscle cells." Pardee,¹ while emphasizing the daily variations in T-wave and R-T interval during the acute stage of rheumatic fever, states "A few patients, especially those with evidence of pericarditis show the peculiar upward convexity of the S-T interval followed by a downward T-wave, the 'coronary' T." The first case described in our report gave no clinical evidence of pericarditis. Of the other two, one presented the typical to-and-fro friction rub for only a very brief space of time, and at no time was there felt to be pericardial effusion in any of these patients. From a review of the literature and from our own observations we find that cases in which clinical evidence of pericarditis is lacking present T-wave alterations similar to those in which pericarditis is known to be present. Clerc, Levy and Vialard¹⁰ described isoelectricity or negativity of T-waves in 19 per cent of a series of 57 cases studied, and described one case in which the S-T interval had a high take-off in all leads. Shapiro¹¹ studied 119 cases of quiescent rheumatism in children and in adults, and concluded that changes in the S-T portion of the electrocardiogram are similar to, but of less frequent occurrence than those in active rheumatism. His control group of 50 normal cases presented only very negligible variations in repeated electrocardiographic studies. Vialard¹² found that out of 63 cases of active rheumatism studied, only 14 presented no electrocardiographic alterations and that there were T-wave changes in 18 of these cases. He did not, however, note characteristic alterations of the S-T segment other than those connected

with abnormalities of the QRS or T. He emphasized the importance of the electrocardiogram for early diagnosis of rheumatic disease, especially when its appearance is atypical such as in cases presenting pulmonary or abdominal symptoms. Vialard quotes from a French clinician, Besnier¹³ who, in 1877, wrote so significantly of the involvement of the myocardium in acute rheumatic fever, that we have felt it pertinent to present a translation of his remarks at this point. "The heart muscle is generally, one may say always, affected to some degree in the course of acute articular rheumatism. This affection may represent an advanced degree without any considerable concomitant lesion of the endocardium or pericardium. If the heart is affected by endocarditis or pericarditis then there is even much more reason to assume that the whole heart is diseased. This fact one has indeed quite forgotten and one is too much inclined to assume that all organic lesions of the heart in rheumatic disease have their origin in the endocardium and pericardium. One might call this whole condition rheumatic carditis, if this expression does not sound too antiquated."

Heiles¹⁴ definitely states that a curving of the R-T segment, either convexly or concavely, to any marked degree cannot occur in a normal heart. Having noted alterations during rheumatic infections similar to those of coronary disease, he accounts for the upward convexity or concavity on the ground of hyperfunction or hyperirritability of a portion of the ventricular muscle. He believes that if the injury to the muscle is of an inflammatory nature, the ventricular complexes will return to normal in a relatively short time. But if there is an area of necrosis such as follows an occlusion of a coronary artery, there will be a lasting dysfunction of the necrosed area. He notes that rheumatic infection is not followed by a sharp T-wave inversion coming late after the time of injury such as is caused by the scarring which follows thrombosis. Slater^{15,16} published three cases which gave the clinical signs of coronary occlusion. The first two cases showed first an elevation of the R-T interval in Leads I and II, this was followed by inversion of the T-wave, which eventually became upright again. In the third case, which had several recurrent attacks, the following changes were observed in addition: Absence of isoelectricity of the R-T segment, flattening of the T-wave, low take-off of the S-T segment in Lead II.

Sebastian¹⁷ presented a statistical study of 26 cases showing that in 15 of these cases some change in the S-T segment occurred in one or more leads, that in one or more leads a negative T-wave appeared in 11 cases, a diphasic T in seven cases, a low voltage T in 16 cases, that there was absence of T-wave in one case, that the T began above the basal line in at least one lead in four cases, and that the ascending branch of the T-wave was oblique and thickened in one or more leads in four cases. Additional statistical data on this subject are given by Lukomski¹⁸ who studied 100 cases of initial or recurrent attacks of acute rheumatic fever and who found negative T-waves in 13 of these cases. He noted that this change occurred usually at the height of the disease and that in eight of the cases the T

became positive again within 10 to 30 days. He noted furthermore the similarity of the upward directed S-T period to that caused by coronary disease but believes these changes are due to Aschoff bodies in the myocardium. Lian and Calcena¹⁹ reported that three out of 28 cases studied showed negativity of T-waves in one or more leads, but did not note alterations of the S-T interval. Master and Romanoff,²⁰ in a recent publication, reported that 53 out of a series of 63 cases of acute rheumatic fever studied, showed some variation in the RST portion of the electrocardiogram. T-wave changes occurred in 29 of these.

We are convinced from a review of the literature on this subject, as well as from our own observations, that R-T or S-T alterations of the electrocardiogram are as characteristic, though not pathognomonic, and probably of quite as frequent occurrence in acute rheumatic fever as the better known alterations in conduction and rhythm. Not only is T-wave inversion or isoelectricity of diagnostic import, but in addition the alterations in the point of T-wave origin with a consequent deformity, shortening or entire absence of an isoelectric R-T segment may be characteristic. These electrocardiographic deformities which are so similar to the deformities of coronary disease suggest that the underlying pathological processes should be looked for in the coronary circulation and a consequent interference with myocardial blood supply, a view-point which has been emphasized by Slater.^{15, 16}

The rheumatic process manifests itself in the heart as a part of a general mesenchymal disease of the organism. The course of the disease shows different stages, which later on may occur simultaneously. The first, an acute stage, is a degenerative-exudative one. It is characterized by edema and fibrinoid swelling of the matrix of the connective tissue, necrosis of muscle fibers and lymph-leukocytic infiltration is often seen. The second, a subacute stage, is often characterized by mesenchymal cell proliferation, the formation of a granuloma, though a diffuse process without this granulomatous formation may take place. The last, a chronic stage, is the process of healing with scar formation.

In this connection the pathology of only the acute and subacute stage is considered and only as far as it concerns the vessels of the heart. The affection of the aortic wall is only mentioned when coronary opening involvement is explicitly mentioned, though rheumatic aortitis (Klotz,²¹ Pappenheimer and VonGlahn,²² Breitenacker²³) may often cause coronary narrowing during the phase of exudative swelling. No mention is made of the degeneration of muscle fibers or of embolic infarction which often accompanies endocarditis (Aschoff,²⁴ Takayasu²⁵).

The following chronological survey will demonstrate, without further comment, the anatomical substratum which may be encountered during the acute and subacute stage. Needless to say, the degree of the pathologic lesions may vary enormously, and the extent of functional interference will

differ correspondingly This functional interference may find its expression in the electrocardiogram

ROMBERG ²⁶—Multiple hyaline thromboses of small arteries and veins Infiltrative periarteritis

RABÉ ²⁷—Proliferative endarteritis of small arteries, often with considerable reduction of their lumen "Mesarterite parenchymateuse"

ASCHOFF ²⁸—All coats of small and medium-sized arteries may be involved in the process of submiliary nodule formation

GEIPEL ²⁹—Rheumatic nodules occasionally narrowing the lumen of vessels Endarteritis of small and medium-sized arteries, the subendothelial fibrinous exudate narrowing or occluding the lumen of the vessels

COOMBS ^{30, 31}—Nodules in media, with unilateral narrowing of the lumen of a vessel Nodular periarteritis Inflammatory patches at the root of the aorta

KLOTZ ²¹—Periarteritis of small vessels

FAHR ³²—Invasion and semilateral destruction of vessel walls by nodules Complete degeneration in focal areas of media

WATJEN ³³—Nodular infiltration of vessel walls with thrombi in diseased vessels

COOMBS ³⁴—Turgescence of the endothelial cells of capillaries and arterioles Endothelial proliferation with disappearance of the lumen of the vessel Thromboses in capillaries, small arterioles and venules and in a main coronary artery

SWIFT ³⁵—Endarteritis with swelling and proliferation Narrowing of vessel lumen by nodules Partial or complete thrombotic occlusion

MCCALLUM ³⁶—Wall destruction of arterioles and of large coronary sinuses with thromboses

PAPPENHEIMER and VONGLAHN ²²—Inflammatory plaque in the beginning of the left coronary artery Parietal thrombus in a large coronary branch Semilateral narrowing of lumen of a vein due to subendothelial infiltration

PERRY ³⁷—Panarteritis of coronary arteries and their main branches, patchy thickening of intima, degeneration and inflammation of media, inflammatory infiltration in adventitia

KLINGE ³⁸—Marked fibrinoid swelling of the intima of small arteries and veins, with narrowing of the lumen Nodules in all wall layers of arteries and veins, intimal cushions

KLINGE and VAUBEL ³⁹—Almost complete occlusion of arteries and veins by swelling and cell proliferation of intima

BREITENECKER ²³—Intima proliferation and thrombosis occludes the right coronary opening and narrows down the left one

SUMMARY

Three cases are reported which showed during the course of a rheumatic infection the following electrocardiographic changes. First, of the S-T (R-T) segment a low or high take-off, a convex upward bowing, a depression, an absence of the isoelectric portion. Second, of the T-wave isoelectricity, low voltage, origin below the basal line, simple inversion, cove-shaped inversion. The electrocardiogram approached a normal form if the rheumatic infection cleared up but even at the stage of complete recovery there was in one case persistence of isoelectricity of the T-waves. In none of the three cases was evidence of a pericardial effusion present. These changes, though not pathognomonic for rheumatic fever, occur rather commonly, as a review of the literature shows. Anatomical studies from the literature are reported which support the conception that the S-T (R-T) and T changes express an alteration of the musculature caused by the effects of the acute infection on the coronary circulation.

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THE GALACTOSE AND UROBILINOGEN TESTS IN THE DIFFERENTIAL DIAGNOSIS OF OBSTRUCTIVE AND INTRAHEPATIC JAUNDICE*

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THE enigma which may confront the internist in the differential diagnosis between mechanically obstructive and intrahepatic (toxic or infectious) jaundice, occurring particularly in individuals beyond the age of 35, is indeed a familiar though often disconcerting situation. Bauer¹ has often emphasized his contention that the galactose tolerance test provides an exact differentiation between these two types of jaundice, for his results were consistently negative in the obstructive form and distinctly positive in the intrahepatic form, unless the latter was of a very mild nature. The observations of other German investigators tended in the main to corroborate these findings. Davies,² although agreeing with these results, felt that no interpretation should be based on this single test of liver function.

In this country, little clinical recognition was accorded these contributions until the papers of Shay and Schloss^{3,4,5} appeared, corroborating Bauer's earlier conclusions. They explained these differences in galactose tolerance on a pathologic basis. In the toxic or intrahepatic form an acute or subacute, diffuse, hepatic, parenchymal damage occurs with a resultant derangement in the carbohydrate function, in the obstructive form, in which hepatic destruction is progressing slowly, the regenerative and reserve powers of the liver permit of a normal carbohydrate function. Recently, in a study of 68 confirmed cases of obstructive jaundice, Banks, Sprague and Snell⁶ found positive results in one-third of the benign group and in approximately 46 per cent of the malignant group, while of 18 cases of acute or subacute intrahepatic jaundice, 84 per cent were positive. They felt that the galactose test might be of value in doubtful cases. Latterly, Tumen and Piersol²⁴ found the test "practically always negative" in obstructive jaundice and positive in the majority of cases of toxic hepatitis and catarrhal jaundice. They regarded it as of definite diagnostic value.

The use of the urobilinogen test in clinical jaundice is based upon the generally accepted view⁷⁻⁸ that urobilinogen is formed from bilirubin by the action of certain putrefactive bacteria of the intestine and is eliminated in part through the kidneys. The disappearance or absence of urobilinogen from the urine in obstructive jaundice has frequently been noted^{1,9,11-16,17-19} since the early observation of Muller,⁷ yet one is able to cull from the literature only a few references directing attention to its potential diagnostic value. Bauer^{16,20} and Wallace and Diamond^{16,17,18} found excessive

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amounts of urobilinogen in the urine during the beginning and end of catarrhal jaundice, and only traces or a total absence during the height of the jaundice, when very little if any bile is being excreted into the intestine. From their studies, Wallace and Diamond,^{16, 17, 18} and later Davies,² concluded that the presence of urobilinogen in the urine points to an intrahepatic jaundice, whereas its constant absence bespeaks an obstructive jaundice.

In the present investigation, an attempt has been made to evaluate the respective merits of these tests, also to ascertain any relative superiority and to determine the virtue of supplementing one test by the other.

MATERIAL AND METHODS

This report deals with the results of studies conducted on a total of 30 patients. Of this series, 16 were cases of obstructive jaundice, which in four was due to a stone and in 12 to a malignant process. The diagnosis in 15 of these cases was confirmed either by necropsy or by operation, and in the other one the clinical diagnosis was definite. Of the remaining 14, there were 12 patients with acute or subacute intrahepatic jaundice, in one of these, the diagnosis was based upon necropsy studies, and in 11 upon the clinical history, the signs and the course which led to ultimate complete recovery. Of the remaining two patients with chronic intrahepatic jaundice (cirrhosis), the diagnosis in one was confirmed at necropsy. Except for these two cases of cirrhosis, only those patients in whom the differential diagnosis between obstructive and intrahepatic jaundice was of primary importance, were selected. The course of the jaundice was followed by repeated determinations of the icterus index. In all cases, studies were instituted as soon as it was feasible, in order to facilitate an early diagnosis.

The technic of the galactose test was identical with that described by Shay, Schloss and Rodis^{3, 4, 5} and was based upon the original work of Bauer. After an overnight fast, the patient voids and the specimen is saved as a control. He is then given exactly 40 gm of pure galactose, dissolved in 500 c c of water and flavored with a few drops of lemon juice. Urine specimens are collected hourly for five hours and placed in separate containers. During the period of the test the patient may drink water if he desires, but nothing else. Each specimen is tested for sugar by the Benedict qualitative method. Those specimens which are positive are mixed and the total amount of sugar is determined by the Benedict quantitative method. An excretion of more than 3 gm of galactose was considered indicative of an intrahepatic jaundice. No diabetics were encountered in this series.

The Ehrlich's aldehyde reaction was chosen for the detection of urobilinogen. The technic consisted of adding 1 c c of Ehrlich's reagent (2 gm paradimethylamidobenzaldehyde in 100 c c of 20 per cent HCl) to 10 to 15 c c of urine. If positive, a red color appeared within 3 to 5

minutes The Wallace and Diamond method of quantitation was used in the early part of this work, but it was soon found that the quantity could be expressed satisfactorily in terms of 1 plus to 4 plus, depending on the depth and rapidity of color formation Normally, urobilinogen excretion, although varying from hour to hour, is greatest when the metabolic processes are at their height, usually in the afternoon Accordingly, urine was obtained before or shortly after lunch and the test was applied immediately In those cases in which urobilinogen was absent, daily examinations were made and at least two late afternoon specimens were examined During the period of observation, no patient received antipyrine or hexamethylamine and the absence of acetone from the urine was ascertained, thereby eliminating pseudo-positive reactions

RESULTS

Acute and Subacute Intrahepatic Jaundice In table 1 are recorded the results of observations on 10 patients with "catarrhal jaundice," one with cinchophen poisoning and one with alcoholic steatosis In the majority, the age was beyond 35, a circumstance which is of special interest to us because of its relationship to the so-called "cancer age" The duration of the icterus from the time of its inception to the day of the galactose test varied from five days to six weeks with a mean average of 17 days In two patients of this group (cases 6 and 10), the jaundice was already subsiding at the time that the galactose test was applied, thereby accounting for the normal response Of the remaining 10 patients, seven excreted galactose in amounts greater than the adopted maximum of normal, in the other three, the excretion was well within normal It is noteworthy that the jaundice in these latter three cases (cases 2, 9 and 12) was at its maximum at the time of the test and that it was particularly intense in case 9 The greatest excretion encountered (6.4 gm) was observed in case 5, at a time when the jaundice had begun to subside (Unfortunately this patient was not seen when the icterus index was at its peak) From these results there appears to be no relationship between the degree of icterus in different persons and the amount of galactose excreted

Case 12 is worthy of special comment, for it exemplifies the point made by Shay, Schloss and Rodis namely, that an extensive and very diffuse process is essential for the production of an abnormal galactose output Even though the galactose test was normal, the liver sections showed a marked alteration of the parenchyma with most of the liver cells filled with large fat droplets and the remaining ones distinctly swollen

In all of the 12 cases, urobilinogen was detected in the urine at one time or another In three instances it was consistently absent during the early period of observation but in none was it absent longer than seven days It always appeared later in gradually increasing amounts It must be emphasized that it is of the greatest importance to examine fresh specimens

TABLE I
Acute and Subacute Intrahepatic Jaundice

| Case | Age | Sex | Duration of Jaundice | Icterus Index | Galactose Excretion (Gm) 4 45 | Urobilinogen* | Diagnosis** | Comment |
|------|-----|-----|----------------------|----------------|-------------------------------|---------------------|------------------------------------|---|
| 1 | 28 | M | 6 weeks | 150 | | Trace | "Catarrhal Jaundice" | Urobilinogen + + + + one week after galactose test |
| 2 | 48 | M | 15 days | 93 | 1 80 | 0+ to + + + + | "Catarrhal Jaundice" | Urobilinogen absent for 1 week. No oliguria, vomiting, diarrhea or dehydration |
| 3 | 27 | M | 2 weeks | 77 | 4 00 | Trace | "Catarrhal Jaundice" | - - - - |
| 4 | 27 | M | 9 days | 118 | 4 90 | 0+ to + + + + | "Catarrhal Jaundice" | Urobilinogen absent for 4 days |
| 5 | 41 | M | 15 days | 45 (Subsiding) | 6 40 | +, later + + + + | "Catarrhal Jaundice" | Icterus index 90, 10 days before galactose test Common duct stone strongly considered |
| 6 | 38 | M | 2 weeks | 37 (Subsiding) | 0 00 | Trace to + | "Catarrhal Jaundice" | Icterus index 64, one week before galactose test |
| 7 | 43 | M | 11 days | 93 | 4 50 | + + + + | "Catarrhal Jaundice" | - - - - |
| 8 | 45 | M | 6 days | 60 | 4 29 | + + + + | "Catarrhal Jaundice" | - - - - |
| 9 | 38 | M | 5 days | 155 | 0 00 | Trace Later + + + + | "Catarrhal Jaundice" | No oliguria, vomiting, diarrhea or dehydration |
| 10 | 55 | M | 25 days | 46 (Subsiding) | 0 80 | + | "Catarrhal Jaundice" | Urobilinogen + for 10 days before galactose test was done |
| 11 | 44 | M | 3 weeks | 126 | 3 60 | + + | Cinchophen Poisoning | - - - - |
| 12 | 36 | F | 4 weeks | 75 | 0 00 | 0+ | Alcoholic Steatosis of Liver (P M) | History of alcoholism and of biliary colic No oliguria, diarrhea, vomiting or dehydration |

* + indicates urobilinogen in urine at one time or another

0+ indicate urobilinogen consistently absent at first and later present

** All are clinical diagnoses except case 12

P M Postmortem

immediately and repeatedly. In cases 2 and 9, which yielded a normal galactose response, such repeated urobilinogen studies proved in retrospect to be of inestimable value, for although these cases simulated catarrhal jaundice clinically, a suggestive history of biliary colic in the face of a negative galactose test (pointing to an obstructive jaundice) proved misleading, and only the urobilinogen excretion curve together with the subsequent clinical course revealed the true nature of the illness. Another case in point attesting its value and indicating the need of a more universal application of the urobilinogen test, is that of patient 10, a man of 55 who presented himself with the symptoms of a painless, progressive jaundice of four weeks' duration, accompanied by a loss of 20 pounds, and concerning whom no definite decision between catarrhal jaundice and carcinoma of the head of the pancreas could be reached. An exploratory laparotomy was deemed advisable, but, because of a consistently positive urobilinogen test, operation was postponed. The subsequent course, characterized by a decline in the jaundice with complete recovery, justified such conservative management.*

Chronic Intrahepatic Jaundice A proved case of cholangiolitic cirrhosis and a clinical case of biliary cirrhosis are included in this category (table 2). The jaundice was intermittent in each instance, and in one had been noted as long as three years before admission. In both, the galactose tolerance test was normal irrespective of the degree of jaundice, and the urobilinogen test was strongly positive.

Obstructive Jaundice This group is represented by 16 cases, in four of which the common duct was occluded by a stone and in 12 by an extrahepatic malignancy (table 3). It is particularly in the latter type of obstruction, so frequently painless in onset, that keen interest attaches to the correct diagnosis and especially prognosis. The age incidence in the cases of malignancy varied from 36 to 77, and the jaundice was of two weeks' to five months' duration, the average being approximately two months. In all 16 cases of obstructive jaundice the galactose excretion was normal. This includes a case of intermittent hepatic fever with jaundice of seven and a half months' duration.

In 10 of the 12 cases of malignancy, urobilinogen was not detected during the entire period of observation, in one, although present in traces during the first five days, it subsequently disappeared and remained consistently absent, in another (case 20), traces were always found, but in this instance the obstruction had not yet become complete. In the cases of obstruction by a stone, urobilinogen was present in varying amounts at one time or another. It is apparent from case 20 that difficulty may be encountered in differentiating an obstructing stone from incomplete occlusion by a new growth, in which instance we must rely upon a carefully

* Because of certain technical difficulties in this case, the galactose test could not be performed when the jaundice was at its maximum. Later, the response was normal but by this time the icterus index was much lower.

TABLE II
Chronic Intrahepatic Jaundice

| Case | Age | Sex | Duration of Jaundice | Icterus Index | Galactose Excretion | Urobilinogen | Diagnosis | Comment |
|------|-----|-----|----------------------|---------------|---------------------|--------------|--|--|
| 13 | 43 | M | 6 months | 18 | (Gm) 2.50 | ++++ | Cholangiolitic cirrhosis with chronic splenic tumor (P.M.) | Jaundice for 6 months before galactose test Intermittent and remittent jaundice for 3 years |
| 14 | 32 | M | 9 weeks | 53 | 0.65 | ++++ | Biliary cirrhosis (Clinical) | Recurrent ascites Intermittent jaundice Liver greatly enlarged Moderate splenomegaly |

TABLE III
Obstructive Jaundice

| Case | Age | Sex | Duration of Jaundice | Icterus Index | Galactose Excretion (Gm) | Urobilinogen | Diagnosis | Comment |
|------|-----|-----|----------------------|---------------|--------------------------|--------------|---|---|
| 15 | 70 | M | 4 months | 67 | 1.37 | 0 | Carcinoma of head of pancreas, obstructive biliary cirrhosis (P M) | Ascites |
| 16 | 64 | M | 3 weeks | 76 | 2.20 | 0 | Carcinoma of common bile duct, obstructive biliary cirrhosis (P M) | — |
| 17 | 77 | M | Unknown | 35 | 0.80 | 0 | Carcinoma of duodenum, compression of common duct (P M) | — |
| 18 | 55 | M | 5 months | 185 | 1.20 | 0 | Carcinoma of head of pancreas, compression of common duct (P M) | — |
| 19 | 72 | F | 5 weeks | 90 | 1.08 | 0 | Carcinoma of head of pancreas, compression of common duct (P M) | — |
| 20 | 36 | M | 3 weeks | 65 | 2.16 | Trace | Carcinoma of common and hepatic ducts Gall-bladder markedly distended (Operation) | Clinical picture of cholelithiasis |
| 21 | 67 | M | 15 days | 63 | 1.00 | Trace 0 | Carcinoma of pylorus with metastases to hilus nodes, compression of hepatic duct (Op) | Urobilinogen in traces for 5 days None thereafter |
| 22 | 50 | M | 15 days | 115 | 0.00 | 0 | Carcinoma of head of pancreas, metastases to and distention of gall-bladder (Operation) | — |
| 23 | 53 | M | 6½ weeks | 65 | 1.50 | 0 | Carcinoma of head of pancreas (Op) | — |

TABLE III (Continued)

| Case | Age | Sex | Duration of Jaundice | Icterus Index | Galactose Excretion (Gm) | Urobilinogen | Diagnosis | Comment |
|------|-----|-----|----------------------|---------------|--------------------------|--------------------|---|---|
| 24 | 55 | M | 2 weeks | 72 | 1 00 | 0 | Extensive carcinoma of gall-bladder and extrahepatic ducts (Operation) | — |
| 25 | 71 | M | 15 days | 75 | 0 55 | 0 | Carcinoma of head of pancreas, metastases to liver (Operation) | — |
| 26 | 68 | M | 3 months | 70 | 0 40 | 0 | Carcinoma of gall-bladder Constriction of hepatic duct by infiltrating tumor (P M) | — |
| 27 | 68 | M | 4 months | 65 | 1 30 | +++ | Large irregular stone in common duct Marked chronic cholecystitis, stones, cirrhosis (Operation) | — |
| 28 | 63 | M | 4 weeks | 123 | 1 40 | + to ++ | Impacted stone in common duct, obstructive biliary cirrhosis (Operation) | Intermittent jaundice 15 years Ascites Splenomegaly |
| 29 | 28 | M | 17 days | 123 | 0 00 | Faint trace | Stones in common duct Marked chronic cholecystitis with cholelithiasis and extensive adhesions around ducts (Operation) | — |
| 30 | 52 | F | 7½ months | 43 | 0 00 | Variable 0 to ++++ | Stone in common duct (Clinical diagnosis) | Typical Charcot's intermittent hepatic fever |

taken history along with the usual clinical and laboratory studies, and, as emphasized by Piersol, Bockus and Shay^{25, 26} and others, upon the presence or absence of cholesterol and bilirubin-calcium crystals in the bile, or, failing in these, prolonged observation of the urobilinogen excretion (case 21) may give us information of a decisive nature.

The persistence of traces of urobilinogen or its subsequent reappearance in experimentally produced complete biliary obstruction has been noted by Wilbur and Addis⁹ and by others^{11, 16, 17, 18, 21}. While these findings did not obtain in our clinical series, such possibilities deserve recognition. From the recent experimental work of Salmon²¹ they appear to be dependent upon the blood bilirubin concentration and the duration of the obstruction. Significant in this respect too, is the presence of bilirubin in the intestinal mucosa of such animals, noted by Gerhardt²² and by others^{11, 23} and presumably indicating a slight leakage of bile pigment through the intestinal wall into the lumen, probably through the casting off of epithelial cells.

COMMENT

From the present study of 30 selected cases of jaundice it is apparent that the galactose test, supplemented by the urobilinogen test, may furnish us with diagnostic data very often of an unequivocal nature. Indeed, Bauer¹⁶ has found these two tests of distinct value, and Davies has referred to the advantage of combining the galactose test with other tests of liver function, including the urobilin test.

In all of our cases of obstructive jaundice, either benign or malignant, irrespective of the duration of the jaundice, the galactose test was negative. In those with complete obstruction, the Ehrlich's aldehyde reagent failed to reveal the presence of urobilinogen in the urine, when the obstruction was incomplete but of a constantly increasing degree, urobilinogen was always detected, though never present in more than traces. In acute or subacute intrahepatic jaundice, if we exclude those cases in which negative results were obtained when the icterus was already subsiding, the galactose test was found positive in seven of the remaining 10. In all cases with this type of jaundice, urobilinogen was present in the urine in variable amounts at one time or another, ultimately appearing in large quantities if the period of observation was sufficiently prolonged.

It is in those cases which do not conform to the rule of the majority that the combined use of the urobilinogen and the galactose tests appears to be of reciprocal value and finds its greatest field of usefulness. Cases 2 and 9 are representative of what was interpreted to be obstructive jaundice, principally on the basis of the normal galactose response, but in which the final picture was elucidated by the repeated, supplementary, urobilinogen studies. Contrariwise, in case 20, an instance of incomplete obstructive jaundice with constant traces of urobilinogen in the urine, it was the nega-

tive galactose test which disclosed the true nature of the morbid process. From this point of view, the report of Banks, Sprague and Snell is of practical interest to us, for although the high percentage of positive results with the galactose test in the obstructive group is at variance with the findings of Bauer, Davies, Shay, Schloss and Rodis, Tumen and Pierson and also with those of the present study, it would seem that the urobilinogen test might be of considerable value in such cases. Finally, we must recall the possibility that a secondary ascending infection of the biliary tract by certain reducing bacteria,^{15, 16, 17, 18} occurring in a case of complete occlusion, may be accompanied by the appearance of urobilinogen in the urine and hence lead us to suspect an intrahepatic jaundice. In such cases the galactose test if negative may be of significant utility.

We may conclude from this study that the urobilinogen and the galactose tests taken individually are truly worthy of clinical acceptance and application. It is more difficult to make final deductions concerning their relative superiority. Yet from an analysis of these cases, the urobilinogen test appears to be more reliable than the galactose test in differentiating intrahepatic from obstructive jaundice. Again, the several factors of error, such as oliguria, dehydration, vomiting and gastric stasis, which may preclude the use of the galactose test or militate against a correct interpretation of its excretion,⁹ do not seem to play a significant rôle in the outcome of the urobilinogen test. The combined use of these tests, however, may provide us with more decisive information and contribute to a more intimate understanding of the nature of the underlying disease.

SUMMARY

1 Galactose and urobilinogen determinations were made on 12 cases of acute and subacute intrahepatic jaundice, two cases of chronic intrahepatic jaundice and 16 cases of obstructive jaundice.

2 Seven cases of acute and subacute intrahepatic jaundice yielded abnormal galactose responses. Of the remaining five with a normal response, in two the jaundice was already subsiding when the galactose test was performed. Urobilinogen was detected in the urine of all cases of this group at one time or another.

3 The galactose test was normal and the urobilinogen test was strongly positive in both cases of chronic intrahepatic jaundice.

4 In the obstructive group the galactose test was uniformly negative. Urobilinogen was absent from the urine of all cases of complete obstruction.

5 Individually, these tests are worthy of clinical acceptance, although from this study the urobilinogen test seems the more reliable.

6 Utilization of both the galactose and the urobilinogen (urinary) tests is advocated in the routine clinical study of jaundice.

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THE PLEURAL AND PULMONARY COMPLICATIONS OF CARCINOMA OF THE ESOPHAGUS^{*}

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INTRODUCTION

ONE of the ways carcinoma of the esophagus may disguise itself is in the form of a chronic pleural or pulmonary infection. This usually is the result of a perforation of the esophagus into the trachea, bronchi, mediastinum, lung or pleura. In some cases, food or fluid is aspirated into the air passages due to the obstruction of the esophagus, or a necrotic lymph node which is the site of metastases may perforate into both the lung and esophagus producing a fistula. In other cases, the trachea or bronchi may be obstructed due to the invasion of the tumor growth or as a result of pressure from enlarged lymph nodes which are the site of metastases. In these, the complications of tracheo-bronchial stenosis arise. At this time, the observations of 17 cases of carcinoma of the esophagus in which there were pleural or pulmonary complications are recorded.

Before proceeding with the details of the cases, it is necessary to point out that the site and frequency of pleuro-pulmonary complications in carcinoma of the esophagus will naturally depend upon the exact type of tumor and its location. It is well known that squamous cell carcinoma of the esophagus ulcerates frequently, and in these cases perforation is seen commonly. Adenocarcinoma of the esophagus, on the other hand, ulcerates less often and produces obstructive symptoms earlier.

The upper third of the esophagus is in close contact with the trachea, the carotid arteries and the recurrent laryngeal nerve. In the medial third, it is in close contact with the trachea, left bronchus, the intercostal arteries, the thoracic duct, the hemiazygos veins, aortic arch, left subclavian artery and left pleura. In the lower third, it is in close contact with the left auricle of the heart, the pericardium and descending thoracic aorta.

It is of some significance that tumors of the esophagus commonly metastasize to the mediastinal lymph nodes. These enlarged nodes may invade the lung or trachea, compress the esophagus at some distance from the primary growth or cause unilateral or bilateral paralysis of the recurrent laryngeal nerves. In a few cases, the cancer may invade the veins so that venous thrombosis or widespread metastases in the lungs or elsewhere are observed.

A summary of the cases is presented in table 1.

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TABLE I
Summary of 17 Cases of Carcinoma of the Esophagus with Pleural and Pulmonary Complications

| Case No | Location of Carcinoma | Site of Perforation | Physical Signs | Anatomical Lesions | Fever | W B C | Duration of Illness | Symptoms | Remarks |
|--------------|-----------------------|-------------------------|---|--|-------------|---------------|---------------------|---|---|
| 1 ♂ 70 | Middle third | Left bronchus | Pleural effusion Left thoracic cavity | Bronchopneumonia left lower lobe | 98.6-101.5° | 16 800 | 7 months | Epigastric pain Dysphagia Coughing following ingestion of food Hematemesis | Hematemesis caused death |
| 2 ♂ 62 | Middle third | Trachea | Bilateral bronchopneumonia | Bilateral bronchopneumonia | 98.6-100.0° | 19 800-20 720 | 5 months | Epigastric pain Dysphagia Regurgitation of food Coughing following ingestion of food or water Purulent sputum | Recurrent laryngeal paralysis |
| 3 ♂ 50 | Middle third | Trachea | Mediastinal widening Rales over both lower lobes | Bilateral suppurative bronchopneumonia | 99-101° | 12 000 | 5 months | Dysphagia Coughing following swallowing Pain in mid sternum | |
| 4 ♂ 72 | Middle third | Left bronchus | Pleural effusion Left pleural cavity Bronchopneumonia left lower lobe | Diffuse bronchopneumonia left lower lobe Pleural effusion | 99-102.5° | 16 800-32 000 | 7 months | Pain in epigastrum Dysphagia Coughing following swallowing | Cirrhosis of liver Metastases to glands at hilum of left lung Hematemesis caused death |
| 5 ♂ 53 | Middle third | Trachea | Superior mediastinal mass | Bilateral bronchopneumonia | 101-102° | 9 000 | 9 months | Hoarseness Dysphagia Coughing following swallowing | Recurrent laryngeal paralysis, right side Mass in superior mediastinum Enlarged glands above right clavicle Perforation observed in trachea with bronchoscope |
| 6 ♂ 59 | Lower third | Left lower lobe of lung | Lung abscess left lower lobe Solidification of left lower lobe | Lung abscess left lower lobe | 99-103° | 18 000-22 000 | 9 months | Dysphagia Pain in chest Cough Copious amounts of sputum | Clubbed fingers Elastic tissue in sputum |
| 7 ♂ 70 | Middle third | None | Signs of solidification of left upper lobe | Lung abscess left upper lobe Narrowing of trachea and left superior bronchus | 99-102° | 12 000 | 8 months | Pain beneath manubrium Coughing after swallowing | Fatal hematemesis Ulceration of vessels |
| 8 ♂ 68 | Upper third | None | Signs of solidification and cavity formation in left upper lobe | Lung abscess left upper lobe Direct extension of infection from cancer to lung | 99-101° | 10 000 | 7 months | Loss of weight Substernal pain Cough and expectoration No dysphagia | Metastases to lung—pleura—peritoneum |

TABLE I (Continued)

| Case No. | Location of Carcinoma | Site of Perforation | Physical Signs | Anatomical Lesions | Fever | W B C | Duration of illness | Symptoms | Remarks |
|---------------|-----------------------|-----------------------------------|--|--|-----------|--------------|---------------------|--|---|
| 9 ♂ 50 | Lower third | Right lung and pleura | Signs of solidification and fluid—right lower lobe | Pneumonia with abscess formation, right lower lobe. Empyema, right pleural cavity. | 99–102.5° | 14 000 | 7 months | Dysphagia. Cough. Epigastric pain. Coughing following swallowing. Pain in right chest. | |
| 10 ♂ 52 | Lower third | Right lung | Rales and dullness over right lower lobe. | Abscess cavity in upper part of right lower lobe. | 100–102° | 13 000 | 2 months | No dysphagia. Cough with copious amounts of sputum. | |
| 11 ♂ 63 | Upper third | None | Solidification of right upper lobe. | Pneumonia and gangrene of right upper lobe. Acute fibrinous pleuritis. | 98–101° | 12 000 | 6 months | Dysphagia—6 months. | Colitis and peritonitis. |
| 12 ♂ 46 | Lower third | Right pleural cavity | Pleural effusion, right side. | Empyema, right pleural cavity. | 99–101° | 26 310 | 2 months | Pain in right chest. | Tuberculosis of pleura. |
| 13 ♂ 52 | Middle third | None | Cervical glandular enlargement. | Multiple metastases in lungs. | 98 | 11 000 | 4 months | Cough and expectoration. Dyspnea. Swelling of neck. | Metastases to cervical and axillary lymph nodes, lungs. |
| 14 ♂ 51 | Middle third | None | Tracheal stenosis. Bilateral bronchopneumonia. | Bilateral bronchopneumonia. | 102–104° | 8 350 | 5 months | Dysphagia. | Recurrent laryngeal paralysis. |
| 15 ♂ 42 | Middle third | Mediastinum | No pulmonary signs. | Carcinoma of esophagus. Ulceration and perforation. Mediastinal abscess. Acute pericarditis. | None | 10 000 | 6 months | Acute symptoms of mediastinitis one day. Dyspnea. Liquid cyanosis of upper half of body. | |
| 16 ♂ 58 | Lower third | Upper third. Necrotic lymph node. | Dyspnea. Tracheal obstruction. Fixation of trachea. Mediastinal tumor. | Carcinoma of esophagus with ulceration in lower third. Necrotic lymph nodes perforating esophagus and communicating with the right upper lobe. | 99–103° | 11 400 | 4 months | Weakness—14 weeks. Hoarseness—12 weeks. Loss of weight. Pain and cough. | Obstruction to esophagus in upper third due to lymph nodes—no obstruction at site of tumor. |
| 17 ♂ 60 | Middle third | Bifurcation of trachea. | | Tracheo-esophageal fistula. Pneumonia—R L L R M L. | 101–103° | 9 000–13 700 | 7 months | Dysphagia—2 months. Anorexia—7 months. Cough and expectoration—1 month. | |

The lesions responsible for the pulmonary and pleural signs are summarized in table 2, and the anatomical findings are listed in table 3

TABLE II

Lesions Producing Pulmonary or Pleural Signs in 17 Cases of Carcinoma of the Esophagus

| | | | |
|-----|--|---|----|
| I | TRACHEAL AND BRONCHIAL OBSTRUCTION | | 2 |
| | 1 Direct invasion of tumor | 1 | |
| | 2 Pressure and invasion of metastatic lymph node | 1 | |
| II | PERFORATION OF CARCINOMA | | 12 |
| | 1 Trachea | 4 | |
| | 2 Right lung or pleura | 3 | |
| | 3 Left bronchus | 2 | |
| | 4 Left lung | 2 | |
| | 5 Mediastinum | 1 | |
| III | NECROTIC LYMPH NODE PERFORATING ESOPHAGUS AND LUNG | | 1 |
| IV | ASPIRATION OF INFECTED MATERIAL INTO BRONCHI | | 1 |
| V | MULTIPLE PULMONARY METASTASES | | 1 |

TABLE III

Anatomical Findings in 17 Cases of Carcinoma of the Esophagus

| | | | |
|-----|---|---|---|
| I | PLEURAL EFFUSION | | 2 |
| | Left | 2 | |
| | EMPHYEMA | | 2 |
| | Right | 2 | |
| II | BILATERAL BRONCHOPNEUMONIA | | 4 |
| | UNILATERAL BRONCHOPNEUMONIA | | 2 |
| III | LUNG ABSCESS | | |
| | Left lower lobe | 1 | |
| | Direct extension | 1 | |
| | Left upper lobe | 2 | |
| | Bronchial obstruction | 1 | |
| | Direct extension | 1 | |
| | Right lower lobe | 3 | |
| | Direct extension | 2 | |
| | Tracheal-broncho fistula | 1 | |
| | Right upper lobe | 2 | |
| | Aspiration | 1 | |
| | Esophageal perforation from metastatic lymph node | 1 | |
| IV | MEDIASTINAL ABSCESS | | 1 |
| V | PERICARDITIS | | 1 |

COMMENT—GENERAL FEATURES

All of the patients were men between the ages of 50 and 72 years. The primary lesion was located in the middle third of the esophagus in ten, in the lower third in five and in the upper third in two. The duration of the disease varied from two to nine months after the onset of the first symptom indicating disease. Once pulmonary or pleural signs became manifest there was fever varying from 98.6° to 103° F or higher, and a leukocytosis between 9,000 and 32,000 per cubic millimeter. The symptoms and signs varied in accordance with the type of anatomical lesion and are discussed separately.

Perforation of Carcinoma of the Esophagus into the Trachea or Bronchi
In the group of cases reported here the trachea was perforated in four cases and the left bronchus in two. In all of them, the carcinoma arose in the

middle third of the esophagus. The symptoms and signs that developed following this complication were highly characteristic and consisted of *paroxysms of coughing and suffocation following the ingestion of fluid or food*. They were due to the passage of foreign material into the trachea or bronchi from the esophagus. After these symptoms and signs had been present for a varying period of time, evidences of pulmonary infection appeared, such as pneumonia or abscess formation. When the fistula was between the trachea and the esophagus the signs were either unilateral or bilateral, when there was a broncho-esophageal fistula the signs were unilateral, the side affected depending upon the bronchus perforated.

The details of an illustrative case of tracheo esophageal fistula are recorded in case 1.

CASE I

A man, 60 years of age, was admitted to the hospital, complaining of difficulty in swallowing. Seven months before admission anorexia had begun, and two months before entry he noticed dysphagia and the regurgitation of solid food. This had increased until he could swallow only liquids. The examination at this time revealed evidence of loss of weight and a narrowing of the lumen of the esophagus at about the bifurcation of the trachea. Following a liquid diet and tincture of belladonna the patient's symptoms were relieved somewhat for about two months. Then the symptoms of dysphagia became worse and attacks of coughing developed following the ingestion of liquids. There was dull pain beneath the sternum which was increased by coughing. The cough was soon accompanied by the expectoration of dark-colored, foul-smelling sputum which was blood-tinged. For one week he had been hoarse. Examination at this time showed fever, emaciation, pallor, moderately enlarged lymph nodes in the supraclavicular fossae, fetor oris, impaired resonance and many fine rales over the right middle and right lower lobe, with bronchial breathing. Roentgen-ray examination showed infiltration of the lower half of the right lung. The white blood cell count was 10,000 per cubic millimeter. The sputum was foul-smelling and abundant, and there was moderate anemia. The clinical course was one of progressive failure, with high irregular fever, loss of weight and the signs of a diffuse suppurative pulmonary disease.

Necropsy showed a squamous cell carcinoma of the middle third of the esophagus which had perforated the trachea at the bifurcation, and pneumonia with abscess formation of the right middle and lower lobes.

Briefly, then, this case illustrates the sequence of events when a carcinoma perforates into the trachea at its bifurcation.

Inasmuch as carcinomata of the esophagus are most common in its upper and median third, it is not surprising that the trachea or bronchi are often invaded or perforated by the tumor. From general experience,^{1, 2, 3} it is commoner to observe perforation of the trachea than of the bronchi, and when the latter are involved either one may be perforated. The left usually is perforated directly by the tumor mass, whereas the right is more often invaded by an abscess from the mediastinum which has resulted from perforation of the esophagus. In the cases collected by Zenker and Ziemssen³ the right bronchus was involved more often than the left.

Perforation of the Carcinoma of the Esophagus into the Lungs or Pleural Cavities The lungs or pleurae were the site of infection in five cases due to perforation of the esophagus and the direct extension of the infection into these structures. In four, the carcinoma arose in the lower third of the esophagus and the perforation caused right-sided empyema in one, abscess of the right lower lobe in two with empyema in one, and an abscess in the left lower lobe in another. In the remaining case, the upper third of the esophagus was perforated and the left upper lung lobe invaded. Aside from these cases in which perforation of the carcinoma was responsible for the pulmonary complication, a sterile pleural effusion was observed in two patients with a broncho-esophageal fistula and a bronchopneumonia.

From these cases, and others reported in the literature, the right lung or pleura is more often involved than the left when a carcinoma of the lower third of the esophagus perforates. The same is true when a pneumothorax occurs as a complication. The following case illustrates the course of events when the lung is invaded by a perforating carcinoma.

CASE VI

A man, aged 59 years, complained of "cough and stomach trouble." Nine months before admission he began to notice anorexia and a burning sensation in the lower part of the left side of his chest which came on soon after eating. Six months after the onset of symptoms he developed pain in the left side of the chest on respiration. The cough increased and was productive of large amounts of foul-smelling mucopurulent sputum. At the same time he noticed increasing difficulty in swallowing so that only liquids could be taken with ease and comfort. Upon examination, it was found that he had lost weight and coughed frequently. There was distinct clubbing of the fingers and pallor. Over the left lower lobe posteriorly there were dullness and rales. Roentgen-ray examination revealed slight cloudiness of the left lower lobe. The red blood cell count was 4,000,000 per cubic centimeter, the hemoglobin 65 per cent and the white blood cell count 22,000 per cubic millimeter. The sputum contained elastic tissue. High, irregular fever developed and the signs at the left lower lobe became more extensive with areas of solidification which were confirmed by further roentgen-ray examinations. The presence of a fistula between the esophagus and lung was established clinically by having the patient swallow capsules containing carmine, and then observing carmine in the sputum as long as three days later. The lesions progressed and the patient died. Necropsy showed a carcinoma of the lower third of the esophagus invading the left lung with abscess formation in the left lower lobe and metastases to the subdiaphragmatic lymph nodes.

This case illustrates, then, the results of a perforation of the lower third of the esophagus with an invasion of the left lower lobe, bronchopneumonia and multiple abscesses.

Tracheal or bronchial obstruction may arise as the result of a direct invasion of an esophageal tumor, or of a lymph node involved by a metastasis compressing either the trachea or bronchi. Three examples of these complications were observed. In all, the signs of tracheal or bronchial stenosis were present. In the case of tracheal obstruction, bilateral bronchopneumonia developed as a complication. In the patient with bronchial

obstruction, an abscess of the lung appeared. The following case is illustrative of tracheal stenosis resulting from an enlarged lymph node, containing tumor, in a patient with a carcinoma in the lower third of the esophagus.

CASE XIV

A white man, 51 years of age, entered the hospital complaining that for the past four months food had repeatedly caught in his throat. The difficulty in swallowing had increased progressively but there had been no regurgitation of food. Upon examination, it was found that he had lost weight and was hoarse. There was paralysis of the left abductor muscle of the larynx, attributed to compression of the recurrent laryngeal nerve. Attacks of coughing coming on after the ingestion of large amounts of fluid may also have played a part in causing hoarseness. The trachea was fixed in the midline; the lungs were normal to physical and roentgen-ray examination. He had a moderate anemia, 3,770,000 red blood cells and 65 per cent hemoglobin, and a normal white blood cell count. Roentgen-ray examination showed a constriction of the esophagus in its middle third which was compatible with the diagnosis of carcinoma. He was treated by dilating the esophagus with bougies and obtained temporary relief from his dysphagia for approximately four months, when he began to have severe attacks of coughing and difficulty in breathing. These attacks followed the swallowing of liquids, and he frequently coughed up small particles of food.

At this time the examination showed an ill man who appeared prostrated and worn. There was obvious dyspnea with wheezing respiration suggesting tracheal obstruction. There was fever, cough, expectoration and hoarseness. There were no enlarged lymph nodes above the clavicle but there was fixation of the trachea to lateral movement, and it seemed to be displaced anteriorly. The lungs showed the signs of a bilateral bronchopneumonia. Otherwise the examination showed nothing remarkable. He failed rapidly and died nine months after the onset of symptoms. Necropsy showed a carcinoma of the middle third of the esophagus which had ulcerated but not perforated. There were large metastatic lymph nodes in the superior mediastinum which had produced recurrent laryngeal paralysis, tracheal and esophageal stenosis. There was a bilateral aspiration pneumonia.

In this case, then, there were two obstructive lesions of the esophagus, one at the site of the carcinoma, the other at the site of the enlarged lymph nodes in the superior mediastinum. The latter had produced, in addition, a stenosis of the trachea which was responsible for the physical signs and the bilateral bronchopneumonia.

In other cases, enlarged lymph nodes in the superior mediastinum, from carcinoma of the lower part of the esophagus, not only compress the esophagus as in case 14, but in addition they may cause perforations in such a manner that there is a communication between the esophagus and the lung. For instance, the following case.

CASE XVI

A man, 58 years of age, complained of weakness and hoarseness of 14 weeks' duration. Accompanying these symptoms there was pain beneath the sternum, an unproductive cough, expectoration of small amounts of sputum, anorexia, progressive weakness and loss of weight. On examination there was hoarseness, stridor, cyanosis of the head with fullness of the neck. The larynx was prominent and fixed so that

it could not be moved laterally. The lungs showed signs of emphysema. There was paralysis of the right abductor muscle of the larynx, moderate increase in the retro-manubrial dullness. The roentgen-ray examination showed a mass in the superior mediastinum. Fluoroscopic examination of the esophagus showed some delay in the passage of barium through the upper third of the esophagus.

Following roentgen-ray treatment over the mediastinum there was an increase in the cough with difficulty in swallowing, and the appearance of solidification and abscess formation in the right upper lobe, high irregular fever and leukocytosis.

Necropsy showed a non-obstructive carcinoma of the lower third of the esophagus. There were metastases in the lymph nodes of the mediastinum and these had invaded the esophagus, the trachea and the lung, and had produced a fistula between the eroded esophagus and the upper lobe of the right lung.

This case illustrates that lymph nodes with metastases not only produce obstruction but that they may cause perforation of the esophagus and fistulous communications.

When the obstruction to the esophagus is in the upper third, the ingestion of food or fluid may be followed by an overflow from the esophagus into the trachea. This produces paroxysms of coughing, and may lead to aspiration lung abscesses, as in case 11.

In summary, then, pulmonary or pleural infections arise during the course of carcinoma of the esophagus by perforation of the growth into the lung, trachea, bronchi or pleura. An enlarged lymph node, due to metastatic tumor, may cause tracheal compression, or it may perforate both the esophagus and lung, producing a fistula. Finally, food may be aspirated into the trachea when there is obstruction.

Carcinoma of the Esophagus with Multiple Pulmonary Metastases

Rarely a carcinoma of the esophagus may remain latent and the manifestations become those of multiple tumor metastases in the lungs, as in the following case.

CASE XIV

A white man, 52 years of age, complained of irritation in his throat, which produced coughing without expectoration, of two months' duration. For six weeks he had had dyspnea on exertion, and a painless swelling on the left side of the neck in the supraclavicular region. Upon examination, it was found that he had lost a considerable amount of weight, and that there were masses of lymph nodes above the clavicles on both sides. The thyroid gland was irregular and nodular, there was increased retromanubrial dullness, but the heart and lungs were negative to physical examination. Roentgen-ray examination of the chest showed numerous round, dense areas characteristic of metastases to the lung. Roentgen-ray studies of the esophagus did not reveal any obstruction. Biopsy of a lymph node from the supraclavicular region revealed a metastatic carcinoma. The patient failed rapidly, and at necropsy a small non-obstructing carcinoma of the lower third of the esophagus with multiple metastases to the lungs and lymph nodes was found.

Differential Diagnosis Two conditions which may be confused with carcinoma of the esophagus and its pulmonary complications are aneurysm of the aorta compressing and eroding the esophagus, and carcinoma of the

lung producing esophageal symptoms. The following two cases are examples.

CASE XVIII

A man, 56 years of age, complained of difficulty in swallowing. Two months before admission he began to notice pain in the right side of the chest and dyspnea. These symptoms increased until one month before entry when he noticed dysphagia for solid food, this increased until it was impossible for him to swallow even liquids. He was well developed but had lost considerable weight. The examination of the chest revealed some dullness at the right base and the signs of a high right diaphragm. There were no signs of an aneurysm of the ascending, transverse or descending part of the arch of the aorta. The heart sounds were clear. Roentgen-ray examination of the chest showed a high right diaphragm with fibrosis of the right lower lobe of the lung. Due to the esophageal obstruction, a gastrostomy was done. Three days later there were signs of consolidation over the lower lobe of the right lung. A day later a to-and-fro friction rub appeared over the heart, and he died the same day.

Necropsy showed an aneurysm of the descending aorta which had ruptured into the mediastinum, forming a hematoma which had caused esophageal obstruction, necrosis and perforation of the esophageal wall and an abscess of both the mediastinum and right lung, and an acute pericarditis.

In this case the pulmonary signs resulted from a perforation of the esophagus due to erosion from a hematoma which arose from a ruptured aneurysm. The signs were predominantly esophageal and pulmonary.

In the following case, the carcinoma arose in the lung and invaded the esophagus causing necrosis and perforation.

CASE XIX

A white man, 80 years of age, complained of difficulty in swallowing. Four months before entry he began to have a severe distressing cough which was non-productive in character. Three weeks before admission he developed dysphagia and was unable to swallow any solid foods, and for one week he had regurgitated both food and water. He had had pain in the left axillary region and back which was exaggerated by respiratory effort. There was progressive hoarseness and loss of weight. On examination he was found to be thin, emaciated and dehydrated. The trachea was deviated to the left and the left side of the chest moved only slightly during respiration. Over the left lower lung lobe there were physical signs of fluid and above this area signs of solidification and of a fibrous pleurisy. The right lung was clear. The heart was displaced to the right but the sounds were clear. There was evidence of a paralysis of the inferior cervical sympathetic ganglion with a Horner's syndrome. There was a moderate anemia and a white blood cell count of 12,000. The pleural fluid was cloudy and contained many leukocytes and pneumococci type V. A gastrostomy was done on account of the dysphagia, and death followed one week later.

Necropsy showed a carcinoma of the left lung invading the mediastinum and esophagus with erosion of the latter, abscess formation in the lung and empyema of the left pleural cavity.

In this patient the esophagus was invaded and perforated by a tumor arising in the lung with resultant infection of both the left lung and pleura.

From the description of these cases, it is manifest that during the course

of a carcinoma of the esophagus a variety of pleural and pulmonary complications may arise which may imitate a large number of primary pleural or pulmonary disorders. In addition, there are a few extrinsic lesions of the esophagus that may produce not only esophageal but pulmonary symptoms and signs as well.

SUMMARY

1 Seventeen cases of carcinoma of the esophagus are recorded in which pleural or pulmonary complications were the outstanding features of the disease.

2 Pleural and pulmonary complications of carcinoma of the esophagus result from perforation of the growth into the trachea, bronchi, lungs or pleurae, or as the result of obstruction of the air passages, of the aspiration of food, or of perforation of the lung by a necrotic metastasis in a lymph node.

3 The symptoms and signs caused by these complications may completely dominate the clinical picture and overshadow symptoms of the primary lesion.

4 The conditions that are to be discriminated from these complications are discussed.

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FURTHER OBSERVATIONS ON THE HEART IN MYXEDEMA¹

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IN a previous paper¹ we presented data dealing with changes in the size of the heart, in the blood pressure and in the electrocardiograms resulting from thyroid medication in myxedema patients. The most striking finding was a shrinkage in the transverse diameter of the heart of from 1 to 7 cm in 20 of the 30 patients observed. Since then 18 additional patients have been studied. Forty-seven teleroentgenograms were obtained and measured. The method of study and the precautions taken were the same as those previously described.

RESULTS

Table 1 summarizes the changes in the size of the heart and in the blood pressure of 18 myxedema patients as a result of treatment. Fifteen of the 18 patients had enlarged hearts, i e the transverse cardiac diameter was greater than half the internal diameter of the chest. The transverse diameter of the heart decreased in all but one instance, the decrease varying from 1.3 to 4.6 cm. The one patient, Mr H T, who failed to show a shrinkage in the size of the heart, had a normal sized heart before treatment, was suffering from angina pectoris and showed bundle branch block by electrocardiogram. He died suddenly at home a year later, probably as a result of coronary occlusion.

A few of the cases require special comment. The second teleroentgenogram in the case of Mrs E D showed the diaphragm to be one and a half spaces higher than in the premedication plate, and in the case of Mrs H E, one space higher. Since a high diaphragm causes the cardiac measurements to be too large, it follows that the actual shrinkage of the heart in these two cases was greater than that observed. In the case of Mrs J N the observed shrinkage was obtained after two weeks. Remeasurement of the heart five and one-half months later showed that the heart had returned to its original size. The reason for this probably lies in the hypertension persisting throughout this period. The patient, Mr J P, developed myxedema as a result of thyroidectomy for hyperthyroidism two months previously. The transverse diameter of his heart shrank after thyroid medication approximately to the size present before operation. This patient is exceptional in that he is the only one in either series who had rheumatic heart disease.

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¹From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital.

The various factors which may play a part in this cardiac shrinkage were discussed in the previous paper. The changes in blood pressure were of the same order as those in the previous series. Fourteen patients had electrocardiographic records made before treatment, and all of them showed some of the typical abnormalities found in myxedema. None of the patients showed evidence of congestive failure.

TABLE I

Change in Size of Heart and in Blood Pressure after Thyroid Medication in 18 Patients with Myxedema

| Patient | Age | Basal Metab Rate | Half Trans Chest Diam | Trans Heart Diam before Medica- tion | Max Heart *Change after Medica- tion | Time Interval for Change | Blood Pressure before Medica- tion | Blood Pressure after Medica- tion |
|---------|-----|------------------------|--------------------------------|---|---|-----------------------------------|--|---|
| | | | Cm | Cm | Cm | | | |
| Mrs E W | 59 | -30 | 13 2 | 18 9 | 4 6 | 11 mo | 190/120 | 208/112 |
| Mrs R T | 55 | -42 | 12 9 | 16 8 | 4 4 | 4½ mo | 125/90 | |
| Mr W D | 48 | -37 | 14 4 | 15 6 | 3 6 | 1½ mo | 120/80 | 110/72 |
| Mrs E H | 36 | -38 | 12 8 | 15 7 | 2 7 | 3½ mo | 88/64 | 106/68 |
| Mrs F B | 57 | -41 | 12 3 | 15 5 | 2 5 | 2 mo | 130/80 | 120/56 |
| Mrs C E | 60 | -23 | 12 3 | 14 5 | 2 0 | 7½ mo | 170/100 | 128/66 |
| Mrs L D | 47 | -46 | 13 1 | 14 6 | 2 0 | 1 yr | 110/65 | 142/90 |
| Mr W A | 18 | -45 | 12 6 | 11 5 | 1 9 | 2 wk | 105/78 | |
| Mrs H E | 39 | -40 | 13 8 | 15 0 | 1 7 | 5 wk | 140/100 | 136/84 |
| Mr P M | 55 | -33 | 15 0 | 15 7 | 1 6 | 1 mo | 112/72 | 116/62 |
| Mrs J N | 67 | -33 | 12 5 | 16 1 | 1 6 | 2 wk | 195/110 | 180/95 |
| Mr J P | 16 | -44 | 13 3 | 14 6 | 1 6 | 9 mo | 114/90 | 120/86 |
| Mrs M T | 42 | -44 | 12 6 | 13 6 | 1 6 | 8 mo | 170/108 | 114/62 |
| Mrs E D | 46 | -35 | 13 7 | 16 3 | 1 5 | 6 mo | 165/104 | 130/90 |
| Mrs N P | 44 | -39 | 12 8 | 11 8 | 1 5 | 6 wk | 110/84 | 100/56 |
| Mrs A L | 46 | -44 | 12 3 | 14 1 | 1 3 | 11 da | 110/80 | 104/66 |
| Mrs H S | 55 | -27 | 12 5 | 15 1 | 1 3 | 14 mo | 170/110 | 216/128 |
| Mr H T | 55 | -29 | 13 8 | 13 1 | -0 4 | 3 mo | 130/98 | 130/80 |

In our previous paper we mentioned the pathological changes in the hearts of five patients, examined post mortem, two of whom had not received any thyroid medication. Recently, we had the opportunity, through the kindness of Dr J H Townsend, to see a patient with myxedema, who died before treatment could be instituted. The heart in this case* was hypertrophied and the myocardium soft and friable. Histologically the muscle bundles and fibers and the connective tissue were widely separated by interstitial edema.

Two papers on this subject which appeared recently are worthy of mention. Hallock² reported two patients with myxedema, one showing gross congestive failure which disappeared under thyroid medication, and the other showing a diffusely dilated heart and a subnormal minute volume output, but no gross cardiac failure. No question can be made of the

* We are indebted to Drs H E McMahon and R Osgood for permission to mention the cardiac findings here. They will publish a complete pathological study of this case in the near future.

facts presented by this author, but we cannot agree that a diffusely dilated heart, accompanied by signs of dyspnea, or a decreased minute volume output are evidence of cardiac failure. We believe, rather, that they are part of the picture of myxedema. The paper of Ohler and Abramson³ concerns itself mostly with the electrocardiographic changes in myxedema. Thirteen of their 21 patients studied showed abnormal electrocardiograms. Cardiac enlargement occurred in seven of the patients with abnormal electrocardiograms, and in all but one the size of the heart diminished under thyroid therapy. However, their data do not warrant the conclusion that mild congestive failure is a frequent clinical finding. It is also difficult to explain why they get electrocardiographic abnormalities in only 62 per cent of their cases, whereas we get abnormalities in all of our cases.

SUMMARY

The changes in the size of the heart and in the blood pressure of 18 patients with myxedema under thyroid medication are presented to supplement the data of 30 patients previously reported. It appears to be characteristic of the heart in myxedema to be enlarged and to undergo appreciable shrinkage as the disease is ameliorated by the administration of thyroid substance. All of the electrocardiograms of these patients taken before treatment showed abnormalities. None of the patients showed congestive failure.

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SMALL INTESTINAL INTUBATION EXPERIENCES WITH A DOUBLE-LUMENED TUBE *

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INTRODUCTION

THE small bowel, excepting the duodenum, has been less extensively and less satisfactorily studied than any other unit of the gastrointestinal system. Various explanations readily suggest themselves: its inaccessibility for direct investigation, the complexity and varied sources of its secretions, the difficulty of obtaining its contents, even in experimental animals, in a normal state of the organ, its elusiveness under the roentgen-ray, its relative immunity from disease. Our knowledge of its secretory and motor functions has rested almost entirely on animal experimentation, on chance observations at operation and on the study of the contents obtained after jejunostomies and ileostomies, methods which, nevertheless, have led to invaluable results.

Several workers^{1, 2, 3} have accomplished small intestinal intubation in man. McClendon and his associates,² in 1920, reported on the hydrogen ion concentration of the contents aspirated from two subjects, but their technic required four days for the tube to reach a level at most four or five feet below the pylorus. None of their methods has led to extensive investigation or important results. Recently, however, we⁴ have developed a technic that seems practical, and that, we believe, may eventually be applied in a more or less routine fashion.

PRINCIPLES OF THE TECHNIC

The passage of the tube along the bowel depends upon the attachment to its distal end of a collapsible rubber balloon which, when distended in the third portion of the duodenum, stimulates peristaltic waves that carry it down the intestinal tract (figure 1). The injection of substances into, and the aspiration of material from, the bowel is provided for by having the tube double-lumened: one lumen for distension and deflation of the balloon, the other, for injection and aspiration.

The tube may be introduced into the duodenum in the usual way or by manipulation under the fluoroscope according to Morgenstern's⁵ technic. By the latter procedure we have sometimes been able to have it enter the jejunum within three to five minutes. When the balloon, in the duodenum, is moderately distended with air under the fluoroscope it usually can be seen to rush immediately to the region of Treitz's ligament. Some massage over

* Read at the Chicago meeting of the American College of Physicians, April 17, 1934.
From the Gastro-Intestinal Section of the Medical Clinic, Hospital of the University of Pennsylvania.

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that point commonly causes it to move slowly around the curve into the jejunum and then to rush 20 to 30 cm farther very quickly. Once the jejunum has been entered, we have found it practicable to allow the patient considerable freedom so long as he continues to swallow the tube at the rate of one centimeter per minute until its proximal end has nearly reached the mouth. At that time he should be re-fluoroscoped to make certain that no coiling of the tube in the stomach has taken place (figure 1)

The outside diameter of the tube is only 6 mm, but each lumen is slightly larger than that of the ordinary duodenal tube, the length which we have



FIG 1 Roentgenogram showing double-lumened tube with attached balloon in small intestine. Note characteristic curves of parts of tube in stomach and duodenum. One lumen of tube filled with 8 per cent sodium iodide solution, balloon partly filled with iodide solution, partly with air.

found suitable for reaching the ileum is nine to ten feet (270 to 300 cm), this allowing the tip easily to advance five to six feet (150 to 180 cm) beyond the pylorus. In one instance with only this length of tubing the balloon reached the middle of the transverse colon (figure 2). Only in that case did we have a balloon pass beyond the terminal ileum, yet when it passed as much as four or five feet below the pylorus it was always beyond the jejunum, because when a barium mixture then was injected no valvulae conniventes could be seen. Such intubation of the intestines has often required not more than three hours, and being accomplished in the morning has allowed the afternoon for experimental procedures.

We have introduced the tube into the small intestine for a distance of 100 cm or more in 75 persons, doing in all more than 100 intubations. At first we failed in about 50 per cent of the attempts, due chiefly to inability to traverse the pylorus within a reasonable time, but, since using the Morgens-tern technic, have been successful in fully 80 per cent. In no instance, with the balloon deflated, have we had any difficulty in removing the tube by mouth. Some of the subjects have been ward or out-patients, others, unemployed individuals to whom we paid small fees.



FIG 2 Roentgenogram showing double-lumened tube in stomach, duodenum, small intestine and large intestine to middle of transverse colon. Barium solution was introduced by tube after tip had reached the transverse colon, and none of barium appears in small bowel.

In making the aspirations the following method has been employed routinely: with the distal end of the tube at the desired level in the bowel, determined by the length of tubing swallowed and by fluoroscopic observation, the balloon is deflated, or it is allowed to remain only slightly distended in order to interfere with the escape of contents beyond the orifices of the collecting lumen. The proximal end of the aspiration lumen is connected with a syphon drainage system arranged to maintain constantly a negative pressure of 60 cm. of water and to allow the collections to be made, under oil, into glass receptacles that may be changed as desired (figure 3).

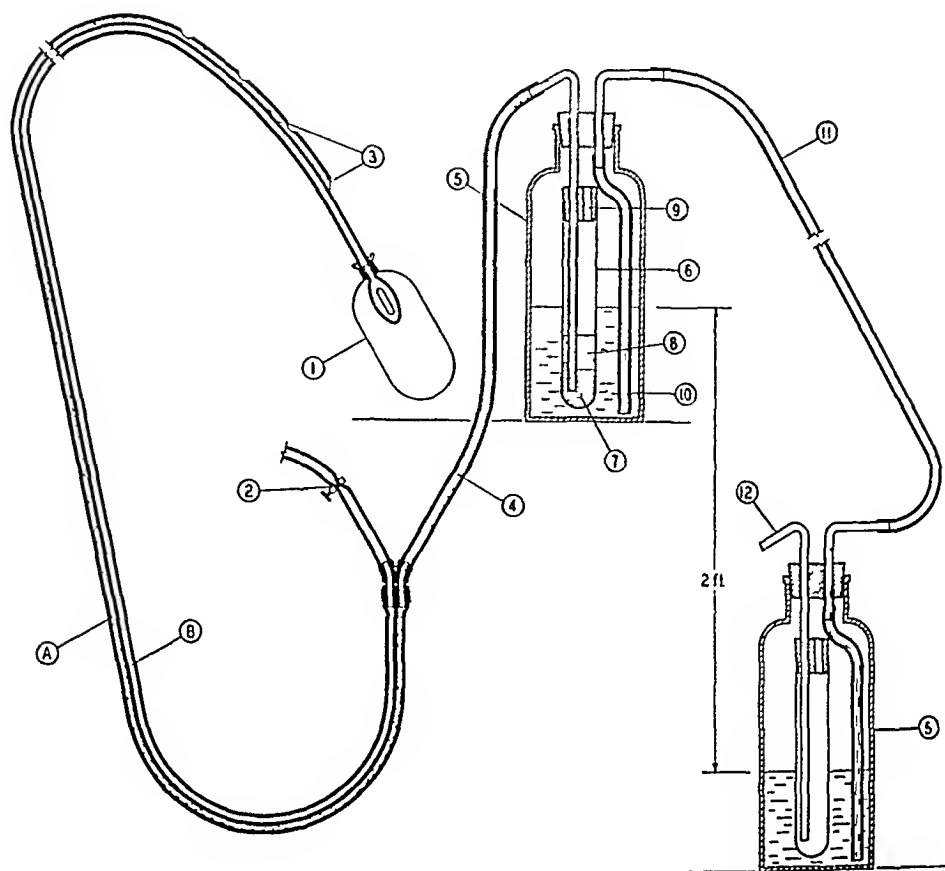


FIG 3 Longitudinal section of double-lumened intestinal tube with attachment to system for making collection of intestinal contents *A* indicates lumen used for aspiration, *B* lumen for inflation and deflation of balloon (1) 2, clamp on proximal tube connected with *B*, 3, perforations, 4 proximal tube connecting *A* with collecting system, 5, bottles partially filled with water (10) and connected by tube (11) so as to maintain constant negative pressure, 6, glass tube for collection of specimen, 7, specimen, 8 oil, originally injected into 4 and *A*, and now overlying specimen, 9, doubly perforated stopper

EXPERIMENTAL OBSERVATIONS AND COMMENTS

The fasting intestinal contents, under the conditions of the method, have come out in small spurts, often of only a few drops, sometimes a few cubic centimeters, with irregular intervals of minutes when no flow occurred. This has suggested the influence of peristaltic waves or of changes in the tonus of the intestinal walls bringing down the bowel small amounts of secretion at a time. Occasionally much larger amounts, 10 to 20 c c, have come through the tube in a continuous rapid flow. This, as demonstrated by introducing a dye into the stomach, has resulted from an unusually rapid passage of gastric contents to the balloon area. Under such circumstances the material collected has been more liquid, lighter in color and of a lower hydrogen ion concentration. Ordinarily the material collected under fasting conditions had the gross characteristics of duodenal fluid, being slightly cloudy, usually of a light yellowish or greenish color, sometimes dark green,

and changing after standing to a perfectly clear solution with a slight, semi-mucoid sediment. Occasionally, but only in achlorhydric individuals with a nasal discharge, small shreds of mucus with pus cells embedded in them have been encountered, but never of sufficient quantity to occlude the tube lumen. This would suggest that the presence of the tube does not lead to irritation of the bowel wall.

Under fasting conditions, with the balloon empty or moderately deflated, it sometimes required one to two hours to secure a specimen of 5 to 15 c c of material, and in 13 cases an average of only 33 c c per hour was obtained. Whether under such conditions very little gastric, duodenal and jejunal secretion occurs and little biliary and pancreatic secretion is ejected from the common bile duct or whether the secretions are largely absorbed as they pass down the jejunum and ileum has not been determined; doubtless both are factors in varying relationship.

In six subjects, when 150 to 450 c c of water had been administered by mouth while the tube was being swallowed, some of them taking most of it during the hour preceding the first collection, the average rate of flow through the tube was actually decreased to 22 c c per hour. Nevertheless, the chloride content in the specimens after the administration of water by mouth was often reduced, indicating that some dilution, probably with proportionate increase of absorption, had occurred. When to one subject 2 gm of decholin were given intravenously, no increase of flow was observed. When 0.5 c c of a 1:1000 solution of histamine was given subcutaneously to each of 10 cases no increase in the rate of flow occurred until the gastric secretion that followed the histamine injection reached the area from which the collection was being made, indicated by the presence in the specimen of vital red, which had been introduced into the stomach at the same time that the histamine was injected. Thereafter the average rate of flow was increased to 64 c c per hour. Also, in several instances, 100 c c of a 25 per cent glucose solution had no effect on the rate of flow until the sugar itself appeared in the specimen, then the average rate of flow was 82 c c per hour.

These observations seem to indicate that the normal content of the small bowel at or beyond the jejuno-ileal junction under fasting conditions is small in amount and that it passes down the tract at a relatively slow rate, that the administration of histamine subcutaneously has little, if any, immediate effect on the volume of the intestinal content, but that eventually, when the gastric secretion of higher acidity that follows the histamine reaches the drained area, a moderate increase in the amount and rate of flow of the intestinal contents occurs, and that a hypertonic glucose solution introduced orally produces a more marked increase in flow, but again only when the solution itself reaches the area of bowel under investigation.

The ultimate increase in the amount of contents after histamine and glucose is undoubtedly due, in part at least, to the added increment from the stomach, but also, since the acidity usually was not appreciably lowered, it is obvious that there occurs, in addition, an increased flow of alkaline material

from the pancreas and perhaps the liver. Although certain animal experiments recently performed in the Surgical Research Department of this University show that after histamine an increase of succus entericus develops in closed intestinal loops, the failure of an increased flow in our human cases until the gastric contents arrived would suggest that the increased flow of intestinal secretion is due to altered chemical conditions in the upper small intestine rather than to a direct action of the histamine.

An extensive study of the chemical nature of the small intestinal contents at various levels and under various conditions is being made in this Clinic by Abbott and Karr, and will be reported upon later. It may be said here, however, that, using a quinhydrone electrode the hydrogen ion concentration has been found in the neutral range (pH 6.6 to 7.3), whether pure fasting contents or material collected after the administration of histamine subcutaneously, decholin intravenously, or glucose or fats by mouth were studied. This is in agreement with the work of Mann and Bollman⁶ and of others on animals. The intestinal fluid maintains its tonicity with blood plasma under most experimental conditions, but it may apparently under certain special circumstances become hyper- or hypotonic temporarily. The tonicity is maintained primarily, according to Abbott and Karr's results, by a balance between the chlorine and carbonic acid anions. The fasting calcium and phosphorus are usually within the blood plasma range.

In regard to the motor function of the intestine Abbott has been able, by connecting the intestinal balloon to a recording apparatus, to secure tracings from the small bowel, and on one occasion from the colon, that indicate changes in pressure incident to the exhibition of certain drugs quite as successfully as they have been obtained in dogs with intestinal fistulae. Thus he has demonstrated nitrite inhibition of intestinal movements, the slower but more prolonged suppression of activity by atropine (figure 4), the increase of peristaltic activity following posterior pituitary extract and the effects of other drugs such as physostigmin and acetyl B methylcholin.

By removing the lateral wall from one lumen of the double tube for a certain distance above its distal end and attaching to the shortened lumen a second balloon it has been possible to secure simultaneous kymographic records from two known sections of the tract. Thus one balloon may be in the stomach or duodenum and the other in the jejunum or ileum at any desired distance from the pylorus.

Furthermore, it has been found practicable to give a subject a small barium meal and so to visualize the stomach and intestine while at the same time making kymographic records. In this way Abbott and Pendergrass have been able to show the effect of peristaltic activity, as recorded, on the intestinal contents, to separate increase in tonus from peristalsis, and to indicate the direction, whether upward or downward, of any particular peristaltic

wave Specifically, by this combined technic they have demonstrated that the gastric retention which follows the exhibition of morphine in man is due to an increased tonus of the muscular wall reaching its greatest intensity not in the pylorus but in the duodenum On several occasions they have observed the barium mixture advance farther than the cap, while a balloon in the portion of the duodenum through which barium was not passing was re-

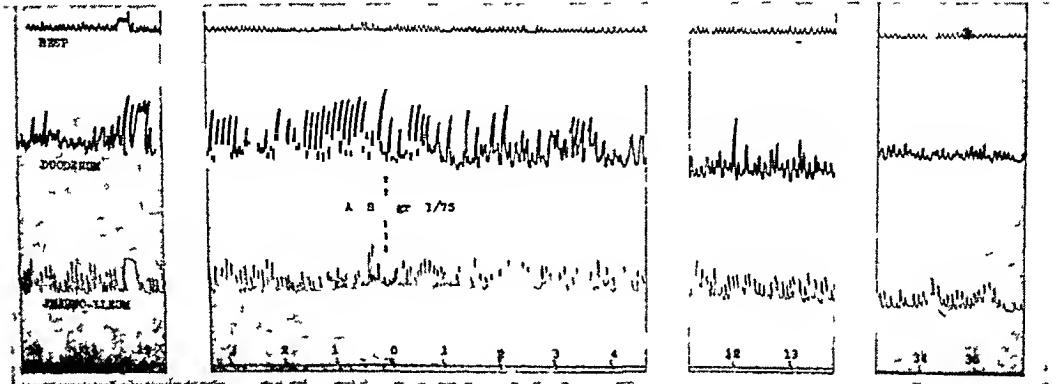


FIG 4 Simultaneous tracings of respiratory rhythm and of duodenal and ileal contractions in a healthy intact human subject Balloons in duodenum and in ileum were attached respectively to the two lumina of double tube, and the ileal balloon was 160 cm below the pylorus Note inhibitory effect of 1/75th gr of atropine, injected subcutaneously, on the duodenum, and its less marked effect on the ileum

cording a prolonged spasmodic contraction They have been enabled by the kymographic records to determine when the enlargement of a segment of small bowel, as seen under the fluoroscope, is due to relaxation of tone and when it is due to forced distention by the passage down the bowel of intestinal contents By omitting the second or proximal balloon and by making continuous suction well above the balloon, they have studied the pressure changes in a segment of bowel independent of any contents coming down from above

CONCLUSION

Thus, we have referred to various experiences with a new method of studying the secretory and motor functions of the human small intestine to indicate the value of the technic, and have presented certain data that confirm results obtained previously only by animal experimentation It is believed that further experience will lead to simplification of the technic, making it available eventually for the study of pathologic conditions of the small bowel

We are indebted to Dr W G Karr, Chemist to this Clinic and Assistant Professor of Physiological Chemistry in this University, for the chemical examinations reported upon in this communication

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DIAGNOSIS AND TREATMENT OF CERTAIN TYPES OF CHRONIC DIARRHEA *

By PHILIP W BROWN, M D , F A C P , *Rochester, Minnesota*

IN fully two-thirds of the cases of chronic diarrhea encountered at The Mayo Clinic there are no definite findings to explain the trouble. These patients usually have drifted from one place to another, have followed dietary fads, and have had the colon flushed. They constitute a puzzling group for both diagnosis and treatment.

There is a so-called harmless type of diarrhea which does not impair the patient's health, this may be present for years and the weight may be normal or even above normal, anemia is not present, and other laboratory studies give negative results. This type may be thought of as the "habit of diarrhea," similar to the "habit of constipation." It should be cared for on a sane, causal basis, and seldom necessitates medication. Of the number of people who lack free hydrochloric acid, it is surprising how few have diarrhea, even more surprising is the small percentage of those who receive benefit by taking acid.

The most common type of chronic diarrhea is that due to neurogenic or psychogenic factors, even in other types, the diarrhea seems to have its origin in shock or nervous upset. A lawyer may have a "running of the bowels" prior to a court trial, and a high-strung, nervous person may have diarrhea when under any emotional strain.

The term "colitis" is especially harmful when applied to this group, it is interesting and amusing to read of colitis as referred to in "The Story of San Michele," but it is another matter to treat patients after they have become obsessed with the idea of colitis. They search for the colitis specialist, the colitis serum, and the colitis diet. Certainly the term colitis should be reserved for cases in which inflammation of the colon is actually present. Some of these nervous people have diarrhea and constipation alternately. The relationship between irregularity of the bowel and nervous strain may not be as apparent as in the purely nervous group of patients. The patients should be instructed and educated in habits of living and eating, but should not be treated for colitis. Wholesome, simple meals, without excessive roughage, and a sane balance between work and play is the ideal program. Seldom is it fully realized, but much more is accomplished by striving for it than by irrigating, vaccinating, or dieting. The judicious use of mild sedatives is practically the only medication that should be considered. "Treat the patient, not the colon" would seem a wise motto.

It is obvious that the treatment of such cases must never be undertaken until all possible causes for the dysfunction of the bowels have been investigated. No matter how neurotic and hysterical the patient may be, the fail-

* Read before the American College of Physicians, Chicago, Illinois, April 17, 1934
From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota

ure to recognize early carcinoma of the bowel, chronic ulcerative colitis, or hyperthyroidism will react most unfavorably on any physician who has diagnosed the trouble as "nervous" Such errors must occur occasionally, but no effort should be spared to rule out organic disease

I have reviewed the records of about 700 patients who have been examined in the past four years and whose condition was diagnosed as diarrhea of uncertain origin Many had acute intercurrent enterocolitis Psychogenic and neurogenic types of diarrhea were most common among the chronic cases But, in addition, three other, smaller but definite groups were observed In one group the condition seemed related to allergic phenomena, in one it was a sequel of an acute infection, and in the third the diarrhea was a prominent symptom of a deficiency disease (table 1)

TABLE I
Chronic Diarrhea

| | Allergic (34 cases) | Postinfectious (24 cases) | Deficiency (20 cases) |
|---|--|-------------------------------------|---|
| Etiology | | | |
| Incidence by sex | Equal | Equal | Females to males, 4 to 1 |
| Onset | Early life, after emotional stress | Following any acute infection | Insidious, dietary deficiency |
| Allergy (hives, hay fever and so forth) | Frequent | No | Occasionally |
| Symptoms | | | |
| Type of diarrhea | Sudden attacks or explosions | Steady or intermittent, watery | Large, bulky, gray, foul |
| General condition | Good | Good to fair | Fair to poor |
| Stomatitis, vaginitis, tetany | No | No | Common |
| Anemia | No | Seldom | Common |
| Treatment | | | |
| Diet | Adequate, elimination diets, keep a food diary | Adequate, low residue | High vitamin, high protein, low residue |
| Drugs | Soricin, calcium, sedatives | Iodine, dihydranol, vaccine calcium | Liver extract, calcium, parathyroid, iron |

ALLERGIC DIARRHEA

In bringing up the subject of allergy, one immediately invites criticism The enthusiast labels most of the cases of nervous diarrhea as allergic in cause, whereas those at the other extreme refuse to consider allergy unless the patient has a violent and prompt reaction following ingestion of a certain food Too much stress can be laid on allergic reactions, but when I re-

viewed this large group of patients with diarrhea, I noted that some patients had an inherent peculiarity which might contribute to the dysfunction of the bowel. Skin tests for sensitivity have not yet proved to be as valuable for ingested as for air borne substances, although the number of positive reactions to foods is increased by use of the intradermal method. Interpretation of results is difficult, partly because all allergic persons are high strung and emotional, although the reverse is not true. Again, it is puzzling to find that people become intolerant to foods formerly well tolerated. Perhaps acute infection or nervous depletion may antedate the explosion of what has been latent allergy. Some people begin to have hay fever in middle life, although they have lived in the same community for years.

I selected only 34 cases for study, because the data on them were adequate, and usually further information had been obtained. During the past four years, economic stress has made it difficult for many patients to remain away from their work for observation and treatment. What follows is based on these 34 cases although some of the statements are general and in the present tense.

In this small group of cases numbers of males and females were equal, and the average age was the late thirties. Most of the patients were aware of peculiar reactions, either hives, hay fever, or digestive upsets since early adult life, whereas nine of them stated they had always suffered from disorders which a physician would interpret as probably allergic. Twenty of the group had had the following allergic phenomena for five or more years: nine had migraine, five, urticaria, one, asthma, and five, hay fever. Allergy in the family was noted only in six cases. Six patients had probable allergic manifestations for one year or less, in four of these, fatigue, acute intercurrent infections, or mental stress seemed to have been precipitating factors.

That the condition may be allergic diarrhea is suggested by the history of rather sudden attacks of loose bowel movements which occur either during the day or at night. A third of the patients normally had loose bowel movements, with occasional attacks of diarrhea. The remainder of the group had the sudden, acute attacks that would last from an hour to several days. The foods which the patients considered factors in producing trouble were chocolate, clams, veal, pork, various fresh fruits and vegetables and fats. Milk was a known offender in five cases. Two patients were sensitive to iron and belladonna. A patient may state "Both my boys and I are scourged by veal and pork." Often the evidence for allergy must be inferred. If the general examination gives negative results, if the patient's weight and color are good, and if direct or indirect evidence of allergic reactions is present, the diagnosis is suggested. Some patients, either on their own initiative or on advice, have eliminated so many foods that they have lost weight and perhaps even have developed some deficiency. This may cause confusion, and caution must be exercised whenever a diet is prescribed.

Treatment This may be both specific and nonspecific. The former refers to omission of the offending foods from the diet. Often, these foods

are not known, and yet a physician dislikes to make a diagnosis of "just nervous diarrhea." It is hard to say why calcium helps some patients. Perhaps an excess supply of it may replace that lost in the stool, or again it may have a definite influence on the metabolism of muscle and nerve tissue. To influence the level of the blood calcium, it must be administered with the patient fasting. I prescribe one heaping teaspoonful of calcium lactate or tri-basic calcium phosphate in warm water three hours after meals, or two teaspoonfuls on arising and on retiring. Morris and Dorst's suggestion of soricin (purified sodium ricinoleate) has been followed in several cases, that is, prescribing a globule of 10 grains (0.65 gm.) to be taken with cold water half an hour before meals. It is still not understood by me what soricin accomplishes, and yet with its use alone or in combination with the calcium I have had gratifying results in several instances. Seven patients have been greatly benefited by this regimen, whereas four others felt that the soricin was of no value. Various regimens, such as calcium with soricin, with parathyroid given orally, with dihydranol or with sedatives have proved beneficial to 13 patients, whereas the condition of six others was not improved. In all instances, an effort was made to see that the diet was sufficient in all food elements. Occasionally, elimination diets, as first suggested by Alvarez, and later carefully worked out by Rowe, were advised but lack of time and funds usually necessitated the patients' following this plan at home. Vaughan recommended keeping a food diary, this is particularly valuable if the patient is intelligent and not too neurotic. Vaughan stressed that the patient must not note just "cheese or salad eaten," but what kind of cheese, the components of the salad, and the kind of oil used in the dressing.

Measures to improve the general physical and nervous stability are as important as drugs and diets. Recreation, work, stimulants, and frequently oral foci must be thoroughly considered. In two cases, the apparent intolerance to certain foods with associated diarrhea was greatly benefited by elevation of the low metabolic rate, soricin also was administered. Both patients insisted that occasional courses of soricin, added to maintenance of the metabolic rate at about minus 5 per cent, were essential to their good health.

POSTINFECTIOUS TYPE OF DIARRHEA

This term is applied to a group of cases in which diarrhea, either steady or intermittent, is a sequel of an acute infection, this may have been appendicitis with rupture, "intestinal flu," or "food poisoning." The actual initial infection is not always definite, and yet I was impressed by the records of 24 cases in which some acute episode had been followed by dysfunction of the bowel. These 24 patients had had diarrhea from three months to 15 years, with an average of about two years. Eleven of them had attacks of diarrhea, whereas 13 had more or less constant looseness of the bowels. Six of them had lost a little weight. Six had moderate secondary anemia, the patient with the anemia of lowest grade had 9.5 gm. of hemoglobin per 100 c.c. of blood. Patients of this group were more definitely

disabled than those of the allergic type. As a rule, the degree of anemia or loss of weight was proportionate to the dietary regimens which had been followed.

Treatment In view of the onset with infection, cultures of stools were made in nine instances, although there was no thought of identifying any organism which initiated the diarrhea months or years previously. Effort was directed toward obtaining the organisms which predominated and preparing a vaccine, as suggested by Dorst and Morris. Five patients considered that much benefit resulted, while four patients were not improved. Three patients were markedly improved following removal of infected tonsils or devitalized teeth. Removal of definite oral foci is always justifiable in any cases in which the cause of the diarrhea is indeterminable, although one should be conservative in promising definite results. Following the use of drugs, success has been none too good. Dihydranol, calcium, sedatives, soricin, parathyroid tablets, tincture of iodine, and inert powders are among the chief drugs that have proved helpful in different cases. One patient may be benefited by iodine, another may not, but is benefited by dihydranol, and so on. I tell such patients that a satisfactory regimen is usually evolved, but that I cannot plan, in advance, the individual program. Even more than in the cases of allergy, the personal and painstaking supervision of the patient is essential to obtain a good result. Seventeen of 24 patients stated months later that their condition was good, whereas the remainder were no better. Among the failures, I was impressed by the associated marked nervous exhaustion and occasionally psychosis. I still do not think that the unstable nervous system is the main factor in these seven cases, but as in other diseases, it is most important. Interestingly enough, five of these seven patients stated that their general health was now good although the diarrhea persisted, perhaps the "habit of diarrhea" had become established.

DEFICIENCY DIARRHEA

I think of this more as a syndrome, rather than a disease entity and of the diarrhea as one of the symptoms. It may be an involuntary type of deficiency as in nontropical sprue, or the voluntary type in which the patient has curtailed his food. If the patient becomes enmeshed in bizarre eating notions, such as faddist diets for ulcer, for diabetes, for colitis, or for purposes of reduction in weight, any of the previously named types of diarrhea may develop into deficiency diarrhea. I have seen severe states of depletion, with marked anemia, great loss of weight, diarrhea, and occasionally edema, which have developed from what seemed originally to be a nervous condition. Certainly it is a nervous diarrhea, but the patient eventually becomes seriously ill. Whether these syndromes of depletion are due to low intake of protein, or to loss of vitamin B, or to some other unrecognized factor, I am uncertain. I am not including cases of celiac disease or idiopathic steatorrhea.

In this group of cases of deficiency diarrhea, there were 20 patients, 16 of whom were women. In the other groups, the sexes were about equally involved. This is too small a group to permit any conclusion, but the preponderance of women is of interest. The average age was in the thirties, and the average duration of intestinal symptoms was about five years. The onset was insidious in half and abrupt in the remainder. Three patients had lost but little weight, whereas 17 had lost from 5 to 60 pounds (2.3 to 27.2 kg). Stomatitis, glossitis, and vaginitis occurred singly or in combination in 10 cases. The stools were watery, often large and bulky, grayish, and occasionally frothy. Cramping of the extremities was present in two cases, in one, it was severe enough to necessitate hospitalization and prompt intravenous injection of calcium. Analysis of gastric contents of four patients revealed no free acid, but administration of hydrochloric acid was of no value.

Secondary anemia was present as a rule. The average value for hemoglobin was about 11 to 12 gm per 100 cc of blood, although it was as low as 5.4 gm in one case. The erythrocyte count was lowered, with a tendency to a high color index. The leukocyte count tended to be low; the highest count in all the cases was 8,500, while in the majority of cases it was about 5,000. In two cases, in which tetany and edema were associated, the value for calcium was 5.6 and 7.0 mg per 100 cc of blood, the plasma proteins were 4.3 mg and 4.1 mg per 100 cc of blood.

Treatment I think success varies directly with the cooperation of the patient and the opportunity to follow each case. Individual treatment is imperative. Of these 20 patients, 12 later reported that they were well, five were improved, and the condition of three was unchanged. In three cases, vaccines from cultures of the stool were tried, were found helpful in one case and were of no value in two others. Calcium was beneficial in 11 cases. In four cases, calcium and parathyroid extract were effective. More recently in the severe cases, especially if anemia was marked, intramuscular injections of liver extract in conjunction with large doses of iron have proved of value. If ferric citrate increased the diarrhea, 4 to 6 gm daily of Bland's mass or 3 gm of reduced iron usually would be tolerated. Foreign protein in the form of intravenous injections of typhoid vaccine was of no value in one case. If depletion and exhaustion were severe, transfusions of blood speeded the convalescence. A diet high in vitamins, high in protein, and yet with minimal residue was instituted. On each tray would be two tablets of Harris' yeast, and 20 to 30 drops of haliver oil with viosterol, or 1 ounce (30 cc) of cod liver oil was given each day. Many of the patients were given anti-amebic treatment, either to ensure that amebic infection was not overlooked, or as nonspecific treatment. No benefit ensued from the use of these drugs.

Relapses are not uncommon. The patient must adhere to this general program for an indefinite period. Nervous shock or acute infection may

precipitate a relapse The margin of safety of these patients is low, and they need more protection than the average patient

CONCLUSIONS

1 The diagnosis of colitis should be reserved for cases in which actual inflammation is demonstrable

2 Neurogenic and irritable intestinal syndromes constitute the largest group of cases of chronic diarrhea

3 Certain persons have inherent peculiar reactions which probably produce or increase intestinal function This is called allergic diarrhea

4 Following any acute infection, diarrhea may develop and persist for months or years

5 As a result of voluntary or involuntary curtailment or omission of certain foods, a deficiency syndrome may result, with diarrhea a prominent symptom

6 Experiences in treatment of the patients in the foregoing groups have been recorded

7 These clinical experiences reveal the need of much investigation by the biochemist, the bacteriologist, and the physician

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EDITORIALS

RELAPSING FEVER IN CANADA

IN 1933 Palmer and Crawford¹ reported six cases of relapsing fever which occurred in the summers of 1930, 1931 and 1932 in the Arrow Lake region of British Columbia. In two of these cases spirochetes were found in the peripheral blood. This constitutes the first report of the occurrence of relapsing fever in Canada.

In the United States the disease has been so seldom recognized in the last fifty years that to most physicians it is little more than a name recalled from student days. Knowing, as we do, that epidemics of the disease have always been associated with times of war and famine, we have perhaps been scarcely grateful enough that it played no part in the mortality from disease in our Army in the World War and that through these recent years of depression it has not broken out among our millions of destitute citizens. Yet it is far from being an extinct disease. It is endemic and at times epidemic in European Russia, Poland, Finland and the Balkan States. In Serbia there are said to have been more than 12,000 cases in the World War. It is prevalent throughout a large part of Africa. The Belgian troops in East Africa in the War suffered heavily. Outbreaks and sporadic cases occur in India, China, Manchuria, and the Dutch East Indies. Nearer home, foci of the disease have been found in Columbia, Venezuela, Panama, and Mexico. In the United States, however, Palmer and Crawford were able to find record of less than 20 reported cases since 1875.

Prior to 1875 the Eastern seaboard was subject to a number of outbreaks of relapsing fever. During the decade from 1842 to 1852 the disease was very prevalent in Ireland, Scotland and England. In June 1844 an emigrant ship from Liverpool landed 18 cases of relapsing fever in Philadelphia. Fifteen of these were studied by Clymer and described in his book on fevers. Similar emigrant groups ill with the disease were seen in New York in 1848 and 1850 and in Buffalo in 1850. In 1869, 1870 and 1871 occurred the only widespread American epidemic. The disease was very prevalent then in New York, and Austin Flint studied over 100 cases on the wards of Bellevue Hospital. In Philadelphia there were over 1,000 cases and scattered cases were seen in the City of Washington and in Maryland, New Jersey and Connecticut.

Though with our present knowledge of the mode of transmission of the disease we should now be in a position to defend our population against similar great epidemics, it cannot be said that it is yet clear why we have been spared further outbreaks since that of 1870.

The first advance in our knowledge concerning the etiology of the disease

¹ PALMER, J. H., and CRAWFORD, D. J. M. Relapsing fever in North America, with report of an outbreak in British Columbia, *Canad. Med. Assoc. J.*, 1933, *xxviii*, 643-647.

came in connection with the epidemic in Continental Europe which preceded and accompanied the American epidemic. In 1868 Otto Obermeier,² a prosector in the Charité Hospital in Berlin, observed a spirochete in the blood of patients during the febrile stage of relapsing fever, though he did not publish this finding until 1873. In the Berlin epidemic of 1872-1873 there were over 100 fatal cases in the Charité Hospital alone, and hence abundant opportunity had existed to repeat the earlier observations. Others speedily confirmed Obermeier's findings but such was still the opposition to the acceptance of the "germ theory" that this early evidence of the etiologic relation of a pathogenic organism to a known fever was for a long time disputed and somehow never was granted the importance it merited. The causal relation of the organism to the disease was more definitely established when Munch, Moczutkowsky (1876), and Metchnikoff (1881) had shown that the injection of spirochetal blood is followed by characteristic relapsing fever in normal human adults.

In 1877-1878 Carter proved that the disease could be similarly transmitted to monkeys. In 1890 Pasternatzky found that the spirochete could live for some time in the body of a leech which had fed on a relapsing fever patient. From this it was an easy step to Tictin's experiments which showed the presence of spirochetes in bedbugs which had fed on relapsing fever cases. Tictin was able to transmit the disease to monkeys by injecting the fluid from crushed infected bedbugs. Though Flugge in 1891 had suggested that the louse might be a carrier of relapsing fever, proof of this was not furnished until a much later date. Sergeant and his coworkers (1910-1911) and Nicolle and others (1912) infected monkeys with crushed lice which had been taken from cases of relapsing fever.

Another important advance in our knowledge of the disease occurred in 1904. For many years a fever of the East and West coasts of Africa, characterized clinically by well defined relapses and apparently due to the bites of ticks, had been known as African tick fever. In 1904 Ross and Milne found spirochetes in the blood of persons suffering with this disease, and Dutton and Todd confirmed that observation and showed that the organisms are transmitted by a tick, *Oimithodorus moubata*.

Since that time many other species of Argasine ticks of the genus *Oimithodorus* have been proved to serve as vectors of relapsing fever in various parts of the world. It has been shown moreover that a number of small animals may act as hosts to the parasite and so constitute a reservoir of the disease. From such animals the disease may be transferred to man by means of the tick as a vector. On the other hand, in epidemic relapsing fever transmission is probably direct from man to man by means of the louse or occasionally the bedbug. The relapsing fever of middle Europe and the Mediterranean littoral is of the louse-borne type, as is much of that of Asiatic countries. The African, Persian and Central American relapsing fever is for the most part carried by ticks.

² OBERMEIER, O. Vorkommen feinsten, eine Eigenbewegung zeigender Faden im Blute von Recurrenkrankheiten. Centrallbl. f. d. med. Wissensch., 1873, vi, 145-147.

Have we since 1875 been spared further epidemics of relapsing fever because of our relative freedom from lice, or merely because no epidemic strain of the organism has developed in our midst? Certainly in our larger cities there are facilities for the transmission of a louse-borne disease sufficient to bring about limited outbreaks were the infection once started. Control measures should, however, guarantee us against a serious epidemic. Perhaps greater interest attaches to the possible spread northward of the infection in animals and ticks, from those central American countries in which it is prevalent. Ticks of the genus *Ornithodoros* are well distributed over our Southwest, and small animals to serve as a host reservoir are not lacking. The occurrence of four cases of relapsing fever in Texas³ due to tick transmission shows that foci of infection already exist. In connection with the British Columbian outbreak, Hearle⁴ published some very interesting observations which suggest that ticks are often transported to points far outside their usual range by attachment to migratory birds. It seems reasonable to expect therefore that in the United States we shall from time to time see sporadic cases of this disease in those people who are exposed to tick bites and that the number of such human cases will be proportionate to the prevalence of spirochetosis in the host animals and in the tick vectors. There exists, as to modes of transmission, a striking analogy between the rickettsial diseases, typhus and spotted fever, and relapsing fever. The gradual spread of the tick-borne Rocky Mountain spotted fever to distant states may be paralleled by relapsing fever.

These facts concerning a rare disease are perhaps of some interest to the internist who may be called upon to recognize it. If he should desire to consult a careful clinical description of the disease he will find that its more recent literature will be of comparatively little help to him in that respect. It is devoted far more to etiology than to symptomatology. A clearer impression of the clinical physiognomy of relapsing fever can be obtained from those who observed the disease with no distracting interest in spirochetes, lice or ticks. No better description can be found than that contained in the masterly article by William Pepper⁵ based on the study and analysis of close to 200 cases seen in the wards of the Philadelphia Hospital during the epidemic of 1870.

VENEREAL DISEASE INFORMATION

FOR A NUMBER of years the U. S. Public Health Service has been publishing, for the information of physicians, health officers, and others, a monthly abstract journal known as "Venereal Disease Information." This

³ WELLS, B., and GRAHAM, G. M. Relapsing fever in Central Texas, Jr. Am. Med. Assoc., 1930, xcv, 1834-1835.

⁴ HEARLE, E. Vectors of relapsing fever in relation to an outbreak of the disease in British Columbia, Canad. Med. Assoc. Jr., 1934, xxx, 494-497.

⁵ PEPPER, W. Relapsing fever, in PEPPER, W., and STARR, L. A system of practical medicine, 1885, Lea Brothers and Co., Philadelphia, pages 369-433.

publication contains usually one original article on a subject of general interest in connection with the venereal diseases and numerous abstracts from the current literature pertaining to these diseases. In the preparation of this abstract journal more than 350 of the leading medical journals of the world are reviewed and abstracts made of the articles on this subject.

The cost of "Venereal Disease Information" is only fifty cents per annum, payable in advance to the Superintendent of Documents, Government Printing Office, Washington, D. C. It is desired to remind the reader that this nominal charge represents only a very small portion of the total expense of preparation, the journal being a contribution of the Public Health Service in its program with State and local health departments directed against the venereal diseases.

REVIEWS

Child Guidance Clinics A Quarter Century of Development By GEORGE S STEVENSON, M D, and GEDDES SMITH 186 pages The Commonwealth Fund, New York 1934 Price, \$1 50

Dr Stevenson, as a director of the Division on Community Clinics of the National Committee for Mental Hygiene, has presented an excellent review of the development of Child Guidance Clinics since the establishment of the first clinic in Chicago in 1909 Since the beginning of the movement over two hundred such clinics have been established in this country, and as is well said by the authors, "The Child Guidance clinic is an attempt to marshal the resources of the community in behalf of children who are in distress because of unsatisfied inner needs or are seriously at outs with their environment

Its service is rendered through the direct study and treatment of selected children by a team consisting of a psychiatrist (who is also a well trained pediatrician), a psychologist, and psychiatric social workers" Therefore, child guidance is essentially a medical problem, and the National Committee for Mental Hygiene has always attempted to keep this movement under medical control

No better comment can be offered than that made in the last paragraph of the book "The Child Guidance Clinic is more than a therapeutic agency It is a tool for synthesizing the most promising approaches to problems of behavior and personality in childhood, and for demonstrating the synthesis to the professions concerned with these problems It is a laboratory in which new leads may be found for the study of the child"

J L McC

Who Shall Survive? A New Approach to the Problem of Human Relations By J L MORENO, M D 437 pages Nervous and Mental Disease Publishing Co, Washington 1934 Price, \$4 00

The author presents what he calls sociometric case studies He states "A sociometric case study endeavors to give an accurate account how an individual or group grows and changes not as an individual or a group singled out but as a part of the community in which it is and not in metric relations only but through the widely ramified actual expressions of the interrelated subjects" There are many diagrams, percentage tables, and rather incomplete case histories The book runs to 437 pages The reviewer confesses it left him in a fog

J L McC

English-German and German-English Medical Dictionary Part I English-German By JOSEPH R WALLER, M D, and MORITZ KAAZT, M D 201 pages, 11×15 5 cm Franz Deuticke, Leipzig and Vienna 1934 Price, M 6—

The English-German part of this dictionary, by Dr Moritz Kaatz, was written as a companion volume to the German-English Medical Dictionary of Dr Joseph R Waller Brief yet reasonably complete for the more frequently used terms, this pocket-size dictionary should be useful to the student of medicine

M F L

Handbook of Physiology By W D HALLIBURTON, M D, and R J S McDOWALL, M B, D Sc vi+971 pages, 16 5×22 cm P Blakiston's Son and Co, Inc, Philadelphia 1933 Price, \$5 50

Halliburton's *Handbook of Physiology* has been considered for years as a valuable text for medical students In this thirty-third edition, Dr McDowall has fol-

lowed the general plan of Professor Halliburton and has presented the subject in a clear and concise manner

The introduction of blank pages at the end of each chapter, so that the student can make notes, is to be commended

It is to be regretted, however, that references to original research publications are lacking

F A R

The Cyclopedia of Medicine By GORGE MORRIS PILRSOL, B S, M D, Editor-in-Chief, and EDWARD L BORTZ, A B, M D, Assistant Editor To be complete in 12 volumes, 9 volumes published to date 19 × 26.5 cm F A Davis Company, Philadelphia 1931 Price, \$120.00

The first nine volumes of this monumental work have been issued and it is expected that the last three will be forthcoming within the next few months The editors have arranged under the alphabetic system articles dealing with the fields of general medicine, surgery, gynecology and obstetrics, and the chief specialties These subjects have been interpreted in a broad sense so as to include the underlying sciences on which our clinical knowledge is based Though the general arrangement is alphabetical the alphabetic system is not followed in the same sense as it is in the dictionary Many topics are dealt with under one main heading, and this heading only is placed alphabetically For example, the section on cardiovascular diseases extends for nearly 400 pages in Volume 3 and constitutes in itself a rather complete monograph on this subject In this same volume the article on the cerebrum and cerebellum takes up 150 pages Similarly in Volume 8 the section on the liver and biliary tract occupies 231 pages In Volume 6, 400 pages are devoted to hematology These will serve as examples In a sense, then, these volumes contain a group of longer sections on the chief fields of medicine, surgery and the specialties between which, according to alphabetic order, fall shorter articles on innumerable subjects

The chief sections are the joint production of a number of authors These authors have evidently been chosen with great care and in general may be said to be the leading authorities in the fields with which they deal To cite only a few at random from the section on hematology Rowntree on blood volume, Barcroft on hemoglobin, Peters on serum proteins, Blooi on lipides, Stadie on blood gases, etc To the reviewer's mind these long sections contributed by so many notable authorities constitute the greatest attraction of the encyclopedia

On the other hand it has not proved possible to confine all discussion of certain subjects under one heading For example, there is a section on the lungs but it deals with only certain diseases of the lungs and with lung surgery, while such subjects as pneumonia and emphysema are dealt with elsewhere under the alphabetic order It is evident that a careful General Index will be a necessity

One feature of the encyclopediac arrangement lies in the inclusion of articles on many special topics concerning which the average physician's collection of books would contain little or nothing Of this type are, for example, the careful articles on the causes of sudden death (37 pages), on deaf-mutism (12 pages), on immature and premature infants (38 pages), and many others The excellent and full treatment of ophthalmological, otological and dermatological topics is notable A serious attempt has been made to present in a brief form general reviews of the clinical sciences, under such headings as bacteriology, immunology, etc The various subheadings under metabolism, each written by an author who has made important contributions to the subject he is discussing, are a good example of the value of these sections The sections on pathological physiology are also very carefully done

In general the articles on the infectious diseases, while for the most part adequate, appear disproportionately short in comparison to the space accorded to less common

conditions Measles is dealt with in 13 pages and malaria in 16 Six pages are devoted to mumps, while the interesting article on monsters takes up 32 pages

There appears also to be an excessive amount of space devoted to drugs, and in certain instances at least the discussion of the therapeutic usages of the drug should be revised to accord with modern practice

The format of the volumes is excellent and the illustrations for the most part well reproduced, especially the cuts from drawings and photographs, which are used very freely Certain of the colored illustrations are valuable, others are more striking than instructive

The reviewer feels that the "Cyclopedia of Medicine" is a very valuable work and that for purposes of reference and general study it will prove an invaluable supplement to the library of any practicing physician The Chief Editor and his Assistant and Associate Editors have performed an immense task in selecting the distinguished contributors to these volumes and in putting through the press so rapidly the nine volumes so far issued The other volumes will be awaited with interest

M C P

COLLEGE NEWS NOTES

NOMINATING COMMITTEE FOR 1934-35

In accordance with the provisions of the By-Laws, President Jonathan C Meakins appointed on May 5, 1934, the following Committee on Nominations

Charles F Martin, *Chairman*, Montreal, P Q
Roger I Lee, Boston, Mass
William J Kerr, San Francisco, Calif
Charles H Cocke, Asheville, N C
Gerald B Webb, Colorado Springs, Colo

It is the duty of the Committee on Nominations "to nominate candidates for the elective offices, Board of Regents and Board of Governors The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective states, provinces or districts which will be represented by the nominees, if elected The list of nominees for President-Elect and for the first, second and third Vice-Presidents shall be submitted to all the Masters and Fellows of the College at least one month before the annual meeting, and the election of all nominees shall be by the members of the College at its annual business meeting This does not preclude nominations made from the floor at the annual meeting itself"

By-Laws, Article I, Section 3

COMMITTEE ON EXTENSION OF POSTGRADUATE EDUCATION

F M Pottenger, *Chairman*, Monrovia, Calif
J H Musser, New Orleans, La
Luther F Warren, Brooklyn, N Y
Ernest B Bradley, Lexington, Ky
Walter L Bierring, Des Moines, Iowa

The above Committee has been appointed by President Jonathan C Meakins in accordance with the following resolution adopted at the meeting of the Board of Regents April 20, 1934

"*Resolved*, that the President appoint a Committee to investigate the advisability of and to formulate plans for the closer organization and greater cohesion of our members in their particular communities or states, such as done by the American College of Surgeons through their sectional meetings, with the object of carrying extension postgraduate medical educational facilities to physicians in more remote locations, and to bring back a report at the next meeting of the Board of Regents"

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the following donations by members to the Library of the College by the authors

Dr Logan Clendenning (Fellow), Kansas City, Mo—1 book, "Behind the Doctor",

Dr Mark Gerstle, Jr (Associate), San Francisco, Calif—1 book, "The Doctor Discusses Your Questions",

Dr S Calvin Smith (Fellow), Philadelphia, Pa—1 book, "That Heart of Yours",

Dr Felix Cunha (Associate), San Francisco, Calif—6 reprints,

Dr Merle Q Howard (Fellow), Wauwatosa, Wis—1 reprint,

Dr Cole B Gibson (Fellow), Meriden, Conn—2 reprints,

Dr Martin J Synnott (Fellow), Montclair, N J—1 reprint,

Dr William F Wegge (Fellow), Milwaukee, Wis—1 reprint,

Dr Joseph Wiener (Associate), Asbury Park, N J—1 reprint,

Dr David O N Lindberg (Fellow), Decatur, Ill—6 reprints,

Dr Hyman I Goldstein (Associate), Caniden, N J—2 reprints

DR JAMES S MCLESTER HONORED

Dr James S McLester (Fellow), for many years a Regent of the American College of Physicians and a member of many important Committees of this organization, was selected as President-Elect of the American Medical Association at the last annual meeting of that Association at Cleveland

Dr Walter L Biering (Fellow and Regent of the College) was installed as President of the American Medical Association at the same session

The Board of Trustees of the University of Pennsylvania recently created a second professorship of medicine and elected Dr O H Perry Pepper (Fellow) to fill it This is the first time in the 169 years of the history of the Medical School of the University of Pennsylvania that there has been provision for more than one professor of medicine Dr Alfred Stengel (Master), present professor of medicine, has been a member of the medical school faculty for 41 years, and although he has reached the age of retirement will continue for a period of three more years through an extension requested by the Trustees

Dr Frederick G Banting (Fellow), for the past 11 years Professor of Medical Research at the University of Toronto School of Medicine, in recognition of his discovery of insulin, was knighted by King George of England on June 3

Dr Samuel E Munson (Fellow), Springfield, Ill, addressed Perry and adjoining County Medical Societies June 8, on the subject of amebiasis Dr Munson, who has served as Councilor for the Fifth Councilor District of the Illinois State Medical Society for the past nine years, was reelected for three years at the annual meeting of that society, held in Springfield, May 15 to 17

At the sixty-seventh annual session of the Mississippi State Medical Association at Natchez, May 8 to 10, the following members of the College contributed papers *Fellows* Dr W S Leathers, Nashville, Tenn, Dr Henry Boswell, Sanatorium, Miss, Dr William Krauss, Meridian, Miss, Dr James S McLester, Birmingham, Ala, and Dr G W F Rembert, Jackson, Miss *Associate* Dr Guy C Jarratt, Vicksburg, Miss

Dr Howard L Hull (Fellow) has resigned, effective July 1, as superintendent and medical director of Oakhurst Sanatorium, Elma, Washington, and has established an office in the Larson Building, Yakima, Washington, where he will enter private practice restricted to diseases of the chest Dr Hull was in charge of Oak-

hurst Sanatorium since September 1, 1923 His successor is Dr Leslie P Anderson of White Haven, Pa

Dr Lea A Riely (Fellow and Governor for Oklahoma), Oklahoma City, as a guest of the Section on Medicine and Diseases of Children of the State Medical Association of Texas, delivered two addresses, "Diabetic Problems" and "The Diabetic Child," before the sixty-eighth annual session of the society at San Antonio, Texas during the week of May 15

Dr Bernard L Wyatt (Fellow) and the Wyatt Research Foundation is erecting in Tucson, Arizona, an ultra-modern building to house the Wyatt Clinic The activities of the Clinic will be restricted to the field of arthritis

Dr D F Milam (Fellow), of the Rockefeller Foundation, New York City, has been assigned work in the Republic of Panama, and will be in Panama City for some months

Dr David Riesman (Fellow), Philadelphia, was the guest speaker at the 59th annual banquet of the Alumni Association of the School of Medicine, University of Cincinnati, on June 14 His subject was "Medical Progress in One Generation"

Dr Harold G F Edwards (Fellow), Shreveport, La, addressed the Texas State Medical Association, San Antonio, May 15, on "Radiation Therapy in Malignant Diseases"

Dr Hyman I Goldstein (Associate), Camden, N J, read a paper on "Hemorrhagic Blood Dyscrasias" before the New Jersey Medical Society at its 168th annual session, Atlantic City, June 6

Dr L F Barker (Fellow), Baltimore, read a paper on pneumonia before the same society on June 7, and the paper was discussed by Dr Goldstein and Dr Robert Kilduffe, of Atlantic City

Dr Ross V Patterson (Fellow), for several years dean of the faculty of the Jefferson Medical College of Philadelphia, was recently appointed by the Board of Trustees of that institution as professor of therapeutics The Alumni Association of Jefferson Medical College, at its 109th dinner early in June, presented the College with a bust of Dr Patterson

Dr James E Paullin (Fellow), Atlanta, Ga, was elected President-Elect of the Medical Association of Georgia at the recent annual session of that society at Augusta

At the unveiling of the portrait of the late Dr D Bushrod James, former Professor of Gynecology at the Hahnemann Medical College, on April 20, Dr James M Anders (Fellow) made an address, representing the medical profession not connected with Hahnemann Medical College or Hospital

Dr James K Hall (Associate) and Dr Beverley R Tucker (Fellow), both of Richmond were elected President and Vice-President, respectively, of the recently organized Section on the History of Medicine of the Richmond Academy of Medicine

Dr Paul D White (Fellow), of Harvard Medical College, Boston, recently delivered an address on heart disease to physicians of central Florida, under the auspices of the Orange County (Fla) Medical Society

Dr J O Elrod (Fellow), Forsyth, Ga , has been elected Vice-President of the Monroe County (Ga) Medical Society for the coming year

Dr Louis Hamman (Fellow), Baltimore, Md , is a Vice-President of the Medical and Chirurgical Faculty of Maryland for the coming year

Dr Robert A Peets (Fellow), Colfax, Calif , was elected President-Elect of the California Medical Association at its annual meeting May 2

Dr Samuel E Thompson (Fellow), Kerrville, Tex , was inducted as President of the State Medical Association of Texas at its annual meeting May 17

The Seventh Annual Graduate Fortnight of the New York Academy of Medicine will take place October 22 to November 2, 1934 The program will be devoted to diseases of the gastrointestinal tract Among Fellows of the American College of Physicians who will present subjects are

Dr Harlow Brooks, New York, N Y
 Dr A C Ivy, Chicago, Ill
 Dr W McKim Marriott, St Louis, Mo
 Dr Charles F Tenney, New York, N Y
 Dr Arthur F Chace, New York, N Y
 Dr William W Herrick, New York, N Y
 Dr Walter A Bastedo, New York, N Y
 Dr Thomas T Mackie, New York, N Y

Dr B S Pollak (Fellow), Medical Director of the Hudson County Tuberculosis Hospital and Sanatorium, Secaucus, N J , has been appointed one of three to represent the United States at the Ninth Conference of the International Union Against Tuberculosis, to be held in Warsaw, Poland, September 4 to 6, 1934 He will discuss Professor Leon Bernard's paper on "The Use and Organization of Tuberculosis Dispensaries"

Dr C J Tidmarsh (Associate), formerly of Montreal, is now connected with the Lahey Clinic, Boston

Dr William H Walsh (Fellow), Chicago, assisted by Dr Clarence O Sappington, recently completed a survey of the Health Department of the City of Buffalo, upon the request of the Board of Health and the approval of the City Council of that City

Dr J A Myers (Fellow), Professor of Medicine at the University of Minnesota, and Dr S A Slater (Fellow), Superintendent of the Southwestern Minnesota Sana-

torium, Worthington, have been elected Directors of the National Tuberculosis Association for the coming year

Dr Kennon H Dunham (Fellow), Cincinnati, Ohio, has been elected President of the National Tuberculosis Association for the coming year

Dr Louis H Roddis (Fellow), Commander (M C), U S Navy, is Editor of the U S Naval Medical Bulletin

Dr J W Torbett (Fellow), Marlin, Texas, was a delegate to the Texas State Medical Association at its recent meeting in San Antonio, and read a paper on "Our Biological Defenses or How Nature Cures"

OBITUARIES

DR CLAUDE EDWARD CASE

Claude Edward Case, of Clifton Springs, N Y, died at Doylestown, Pa, on January 27, 1934, of lymphosarcoma. Dr Case was born at Doylestown in 1893 and received his early education in the public schools there. He attended the medical department of the University of Pennsylvania from which he was graduated in 1917. After serving an internship in the Philadelphia General Hospital he became a lieutenant in the Medical Corps of the United States Army and was stationed at various American camps during the World War. Following his discharge from the army he associated himself with the health service of Cornell University at Ithaca and became Assistant Professor of Hygiene. In 1927, Dr Case joined the staff of the Clifton Springs Sanitarium and Clinic. He was a member of Phi Chi medical fraternity, the New York State Medical Society, and the American Medical Association, and on February 10, 1930, he was made a Fellow of the American College of Physicians.

During recent years Dr Case was particularly interested in the relation of radiology to internal medicine and published several papers in that field. He was known as an unusually kindly physician, one to whom his parents were devoted. For recreation he enjoyed golf and was an accomplished pianist. Dr Case is survived by his widow, Emily Radcliffe Case.

DR WARREN B STONE

Dr Warren B Stone (Fellow), Schenectady, N Y, died March 31, 1934, following a stroke.

Dr Stone was born in Lynn, Mass, in 1876. He received his medical training at Harvard University Medical School, from which he graduated in 1899. Thereafter, he served as intern for a year and a half at St Luke's Hospital, New Bedford, Mass, and then sought postgraduate study at the University of Berlin. He also did postgraduate work at Albany Medical College and Union University. In 1916, he became Head of the Ellis Hospital Pathological Laboratory. During the World War, Dr Stone was commissioned a Captain, but his services were retained in this country rather than abroad, due to his work in controlling the influenza epidemic. It is said that a serum developed by Dr Stone at the Ellis Hospital was very effectively used in controlling the spread of influenza, and that only 1 per cent of the 25,000 to whom the serum was administered contracted the disease.

At the same time that Dr Stone held the position as Head Pathologist of the Ellis Hospital, his ability was also recognized by the county authori-

ties, who made him head of the county pathological work. This laboratory, under his effective administration, became one of the divisional laboratories of the State Department of Health. In 1923, Dr. Stone resigned from his post at the Ellis Hospital to devote his full time to practice and consultation work. He fitted out a private diagnostic laboratory in his home with all modern equipment. During the past two years, he also did the pathological work at the Glenridge Sanatorium. He was also Examiner in Serology for the Civil Service Commission of the City of New York.

Dr. Stone was a past president of the New York State Pathological Society, a member of the Schenectady County Medical Society, the New York State Medical Society, the New York State Society of Pathology and Public Health, and had been a Fellow of the American College of Physicians since 1916.

DR. ADDISON E. ELLIOTT

Dr. Addison E. Elliott (Fellow) of San Diego died April 9, 1934. Dr. Elliott was ill last January with a pulmonary edema for a couple of weeks, recovering from that he worked practically all the time until two days before death occurred.

Dr. Elliott was born in 1875. He received his medical education at Rush Medical College. The first years following were spent in Chicago. About 1914 Dr. Elliott moved to El Centro, California, where he built up a good diagnostic and surgical practice. At a period after the War Dr. Elliott gave up his other work for roentgenology, in which he had been interested for many years, and went to San Diego. Following a year's work in roentgenology at the San Diego County Hospital he became associated with Dr. Lyell Kinney, with whom he carried on in the active work of roentgenology until his death.

Dr. Elliott was made a Fellow of the College in 1930. He was at one time President of the University Club and had been Chairman of the Council of the San Diego County Medical Society, and President of the San Diego Academy of Medicine, in addition to having memberships in other scientific organizations.

Dr. Elliott was a kindly man. He had no malice in his heart but thought kindly of all worthy men. He went out of his way to do acts of kindness that endeared him to all with whom he came in contact. Though he was modest and by nature moderately reticent he took his responsibility as it came to him, meeting his problems with clear decision. He had many friends in the profession in California. In San Diego, his home, he was loved as are all kindly, able men. His death was a loss to the profession and his community.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Governor for Southern California

DR HENRY GREEN

Dr Henry Green of Dothan, Alabama, an Associate of the College, died, after a short illness, on February 22, 1934, of cerebral hemorrhage

Dr Green was born in 1867 and received his M D degree from the University of Alabama School of Medicine in 1892 He practiced in Dothan, Alabama, up to the time of his death Dr Green was past President of the Houston County Medical Society and also of the Medical Association of the State of Alabama For many years Dr Green did a very large practice in his community

He was beloved as a physician and admired as a man He was honest, high-minded, intelligent, and sympathetic In his private life, as well as his professional life, Dr Green was an ideal citizen He was active until about two days before his death and his passing is a loss to the American College of Physicians as well as to the medical profession

FRED WILKERSON, M D , F A C P ,
Governor for Alabama

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BILIARY DYSKINESIA *

By A C Ivy, Ph D, M D, F A C P, and PHILIP SANDBLOM, M S,
Med Lic, Chicago, Illinois

THE trend of modern medicine toward the early diagnosis of disease has led to an increased interest in functional disturbances which may precede or even cause organic changes in structure

In applying this viewpoint to the extrahepatic biliary passages, one may think theoretically of three kinds of functional disturbances, namely, of absorption, of secretion and of motility. Of these, we propose to discuss the disorders of motility or the so-called *biliary dyskinesia*, which may produce biliary stasis and the symptoms of gall-bladder distress or colic in the absence of calculus or inflammation. We shall give only a brief summary of the historical development, the physiologic basis and importance of this subject and point out certain pertinent observations we have made in our laboratory studies of the biliary tract.

Apparently the first clinical reports of gall-bladder colic without stone or infection were made by Krukenberg¹ in 1903 and Borghi² in 1913. These reports provided no explanation and attracted no attention. Undoubtedly many physicians have seen patients who have suffered gall-bladder distress without detectable anatomic cause and have explained the condition as being due to adhesions or to the passage of inspissated bile.

In 1909, the pathologists, Aschoff and Bacmeister³ laid the foundation for further development of the concept of biliary dyskinesia by describing what they called the "stasis gall-bladder." They distinguished two kinds of "stasis gall-bladder," the hypertrophic and atrophic, in which either hypertrophy or atrophy of the wall, especially of the muscle layer, was found in the absence of inflammation or stone formation.

In 1920, Schmieden⁴ in his important work on the "stasis gall-bladder" correlated the pathological with the clinical findings. He called attention particularly to those patients with typical gall-bladder distress in whom the surgeon at operation finds a markedly distended gall-bladder without calculus or inflammation. He thought that the distention of the gall-bladder was the cause of the distress, and that the distention was due to a mechanical

* Read at the Chicago meeting of the American College of Physicians, April 17, 1934.
From the Department of Physiology and Pharmacology, Northwestern University Medical School.

hindrance to the flow of bile from the gall-bladder into the cystic duct. He thought the hindrance was due to an anatomical defect such as a kink, at the junction of the neck of the gall-bladder and the cystic duct (also see Rhode⁵). As is well known, this work was at first accepted with enthusiasm and later subjected to criticism because the hypothetical anatomic hindrance could not always be found.

In the meantime John Beig, the Swedish surgeon, was working on the problem and in 1922 he⁶ suggested that a functional disorder of the biliary passages might be the cause of biliary stasis. This suggestion was supported by his observation of an accompanying hypertrophy of the muscle surrounding the ampulla of Vater. This hypertrophy has also been observed by Westphal,^{13,14} Nuboer⁷ and Newman⁸. Giordano and Mann⁹ have also found hypertrophy of the common duct sphincter in some cases of cholecystitis and peptic ulcer. Nuboer⁷ has reported that the sphincter muscle is found to be hypertrophied in dogs 16 months after cholecystectomy and Westphal¹⁴ has made a similar observation. Before this, however, Oddi,¹⁰ in his classical work, and Meltzer¹¹ (1917) on the basis of physiologic theory had suggested that spasm of the sphincter of the ampulla may be the cause in some patients of biliary colic or icterus (also see Lyon¹²).

The concept of a "functional" cause of gall-bladder stasis has been especially developed and emphasized by Westphal,^{13,14} who, as a result of his experimental and clinical observations, classified and gave a general clinical description of the different types of biliary dyskinesia, their diagnosis and treatment.

Because Westphal's¹³ experimental work on the guinea pig and rabbit led him to produce the first clear-cut classification of biliary dyskinesia, we shall briefly give an account of his observations. It should be pointed out, however, that his observations have not been fully confirmed. (For a review of literature, see Ivy¹⁵). Westphal regards the sphincter of Oddi as being composed of two parts, possessing a different structure and function. The first part consists of a proximal muscular coat which surrounds the antrum beginning at the junction of the duct with the ampulla. The second part consists of a distal group of muscle fibers which surround the papilla. The work of Lueth,¹⁶ which the senior author observed, indicates that this view is probably correct. Westphal reports that when the vagus nerve is stimulated below the diaphragm with a weak current, the gall-bladder contracts, the antral portion of the sphincter manifests peristaltic movements and the papilla relaxes. He views this as being the normal type of response. With a stronger current, he reports that the tone of the gall-bladder is increased, and the movements of the ampulla are very lively. He suggests that this would cause a very rapid emptying of the gall-bladder, which, when it occurs in the human, he calls "hypermotile dyskinesia". When the vagus is stimulated with a still stronger current, he reports that the antral sphincter is thrown into spasm along with the contraction of the gall-bladder. This, he interprets, would cause spastic distention with pain, a condition he calls

"hypertonic dyskinesia" The difference between hypermotile and hypertonic dyskinesia is only one of degree of hypertonicity, and both are grouped under the general heading of "hyperkinetic dyskinesia"

On the other hand, when the splanchnic nerve is stimulated, Westphal reports that the gall-bladder and antral portion of the sphincter relax while the sphincter of the papilla contracts. This, he believes, would cause an atonic distention without much pain, a condition which he calls "atonic dyskinesia"

WESTPHAL'S CLASSIFICATION OF BILIARY DYSKINESIA

I Hyperkinetic

a Hypermotile Increased motility of gall-bladder and ampulla with rapid emptying

b Hypertonic Contraction of the gall-bladder against spasm of the sphincter with *spastic distention* and colicky pain

II Atonic Relaxation or atony of the gall-bladder with spasm of the sphincter of the papilla causing *atonic distention* of the gall-bladder with mild, continuous, "heavy," aching sensation

Lyon¹⁷ has classified the motor dysfunction of the extrahepatic passages into two types, "spastic dysfunction" and "atonic dysfunction," and suggests that in the course of time a spastic sphincter may cause the gall-bladder to become atonic. Smithies¹⁸ has referred to the condition as "physiologic block," and Schmieden¹⁹ has used the term "cholepathia spastica." Newman⁸ has used the terms "spastic distention" and "atonic distention," and cautions against the division of dyskinetic states into hard and fast entities. We agree with Newman's caution.

In regard to this concept, which maintains that biliary distress may result from a motor dysfunction of the extrahepatic passages, two pertinent questions present themselves for answer. First, can the sphincter of the common duct, or the choledocho-duodenal mechanism, contract with sufficient force to prevent evacuation of the contracting gall-bladder? And, second, is it possible for the resulting pressure to produce pain in non-inflamed biliary passages?

In answer to the first question, only evidence obtained from lower animals is available. In the dog it is established that the gall-bladder may contract with a maximum force of about 30 cm. of bile pressure, which is also about the secretory pressure of bile, whereas the common duct sphincter, or the choledocho-duodenal mechanism, may contract and exert a resistance of as much as 80 cm. of bile pressure¹⁵. Thus, it is evident in the dog that a spastic choledocho-duodenal sphincteric mechanism may cause an intra-biliary passage pressure sufficient to block the flow of bile either from the gall-bladder or liver.

In answer to the second question, experimental evidence obtained from normal human subjects by utilizing two different methods for gall-bladder excitation is available.

First, by pilocarpine, a parasympathetic excitant Westphal¹⁴ passed a duodenal tube and initiated gall-bladder evacuation with olive oil. He then injected a relatively large dose of pilocarpine, a drug which in the dog causes gall-bladder contraction with some filling of the cystic duct but no evacuation due to contraction of the common duct sphincter. After the pilocarpine injection, he observed that the flow of bile into the duodenum ceased, following which gall-bladder distress was frequently obtained. This distress was promptly relieved by atropine which abolishes the action of pilocarpine on the gall-bladder and sphincter.

Second, by cholecystokinin, a hormone agency which acts chiefly by direct action on the musculature of the gall-bladder During the past year, the senior author with Voegtlin and Greengard²⁰ has been studying the effect of secretin-cholecystokinin injections on the duodenal secretions in normal human subjects. The plan of the procedure is briefly as follows. The duodenal tube is passed. A number of control samples are obtained. Then a solution containing secretin and a little cholecystokinin is injected intravenously to determine the effect on the volume and chemistry of the duodenal contents. This injection generally produces a copious flow of both pancreatic juice and bile. In one of the first subjects, the following observations were made. After passage of the tube into the duodenum, a flow of bile-stained fluid was first obtained. Then the flow of bile-stained fluid ceased. Apparently a contraction of the common duct sphincter had resulted, shutting off the flow of bile. No distress was experienced at this time. Then the secretin-cholecystokinin solution was injected. A copious flow of pancreatic juice resulted which was not stained with bile. About 10 minutes later, right hypochondrial distress was experienced which gradually became more severe and finally was felt beneath the right scapula. After about 50 minutes, the distress was so severe that relief was sought. It was decided to ascertain if relief might be obtained by the introduction of magnesium sulphate. This was done and a few minutes after the introduction of the magnesium sulphate into the duodenum, the distress subsided and after seven minutes, dark bile was obtained from the tube. Cholecystographic evidence on this subject proved that the gall-bladder concentrated and evacuated normally. The duodenum and stomach were normal. Out of 19 normal subjects studied to date, biliary tract distress has been observed in three under these experimental conditions. This, we believe, constitutes a striking confirmation of Meltzer's¹¹ hypothesis that magnesium sulphate placed in the duodenum may relax the abnormally contracted sphincter of the common bile duct.

Until these observations were made, we were skeptical concerning the claim that pain can be produced in the non-inflamed biliary passages by such relatively low pressures as may be produced by the contraction of the gall-bladder. We were skeptical in this regard because Schrager and Ivy⁴³ had found in the dog that the minimal pressure required to elicit pain by distending the gall-bladder was 54 cm. of water, and by distending the bile

ducts 27 cm of water. However, it is to be noted that the pressure required to elicit pain from the bile ducts in the dog is just about the secretory pressure of bile and the maximum force of gall-bladder contraction. Also, Ivy and Oldberg²¹ observed pain distress with nausea and vomiting in a dog with the cystic duct occluded following the injection of cholecystokinin. Von Bergmann²² has observed that the injection of dehydrocholic acid, which stimulates the formation of bile, into patients with common duct stenosis causes pain. This evidence and our observations on man cited above have convinced us that pain may be elicited from non-inflamed biliary passages by the maximum pressure that may occur in their lumen, provided the pressure is raised rather rapidly, especially in the presence of a tonic musculature.

According to the German school, biliary dyskinesia is due to an abnormal parasympathetic or sympathetic innervation. Newman⁸ and Lyon¹⁷ are inclined to the view that there are constitutional factors which predispose to either of the two types of dyskinesia. Boyden²³ describes three types of responses of the normal human gall-bladder to stimuli, which appear to depend primarily on how the sphincter responds, but has not attempted to relate these types to predisposition to dyskinesia.

In regard to the etiology of this condition, we believe that one must not neglect to consider the duodenum, the tone and motility of which is closely related to the functioning of the common duct sphincter^{16, 24}. For example, Cram and Walsh²⁵ have demonstrated that experimentally induced duodenitis delays evacuation of the gall-bladder, and Shapiro and Kasabach²⁶ have found that a partial duodenal obstruction may also delay gall-bladder evacuation.

Most students of the subject of biliary dyskinesia, as we have indicated above, would place the cause of the functional obstruction solely at the site of the common duct sphincter. However, another possible site should be considered, because it is possible that a sphincter may be located at the junction of the neck of the gall-bladder with the cystic duct. Whether such a sphincter, which has been called the "collum-cysticus sphincter," exists anatomically, is disputed¹⁵. Lutkens²⁷ from Aschoff's laboratory, reports that he was able to find such a sphincter in 75 per cent of human subjects. Certain physiologic evidence submitted by Volborth²⁸ and Potter and Mann²⁹ suggests the existence of such a sphincter. Westphal¹⁴ claims that such a sphincter is present in dogs and derives its motor innervation from the vagus. Careful cholecystographic study in man should in the course of time provide an answer, because, if the "collum-cysticus" sphincter is spastic, the gall-bladder when excited should manifest annular bands of contraction without the expulsion of contents resulting. Whereas, if the common duct sphincter is spastic, the gall-bladder should expel contents and the hepatic ducts become visualized. Both have been reported to occur in dyskinesia patients³⁰⁻³³.

The concept of biliary dyskinesia, which we believe to be established, not only provides an explanation for the "stasis gall-bladder" of Aschoff,

but also provides a mechanism with which to visualize the cause of stasis which predisposes to infection and stone formation. When this is more widely appreciated and recognized, it is not unlikely that the incidence of cholelithiasis, particularly in pregnancy, may be reduced by appropriate prophylactic therapy. The literature on the relation of pregnancy to the evacuation of the gall-bladder is meager (Ivy¹⁵). Westphal^{13,14} and Kalk and Schondube³² made observations which led them to believe that a hyperkinetic dyskinesia was present in early pregnancy. (See also references 23 and 34-39.) But a large series of patients has not been studied. This obviously important topic needs investigation.

This concept also provides a rational basis for gall-stone colic without gall-stones, for so-called "cholecystitis" with a normal gall-bladder at operation, and for so-called "hepatic neuralgia." It is further possible that the presence of an irritable or hypertrophied sphincter of the common duct may explain the recurrence of symptoms in some patients following cholecystectomy. The early relief would be due to the temporary paralysis of the sphincter that always follows cholecystectomy. But, after recovery from the temporary paralysis, the irritable or hypertrophic sphincter may again produce symptoms of biliary tract distention. The recognition of this possibility should emphasize the importance of the medical rather than the surgical management of these patients, although it must be recognized that some dyskinesia patients are benefited by cholecystectomy and some patients with residua after cholecystectomy are benefited by choledochoduodenostomy. In this connection, Aschoff⁴² reports a series of 215 cases in which 25 stone-free gall-bladders were removed, of the 25, seven had residual symptoms accountable for only by dyskinetic processes. (See also reference 40.) It is likely that the number of discouraging results may be fewer when the idea of a functional disturbance is better understood and managed therapeutically by the surgeon and internist.

As indicated in the introduction to this paper, we did not propose to discuss the diagnosis and treatment of biliary dyskinesia. (For discussion of diagnosis and treatment, the reader is referred to the following references 8, 13, 14, 17, 19, 22, 30, 31, 32, 33, 40.) We should state, however, that we do not believe the diagnosis to be simple. The presence of pain in the gall-bladder region with a normal 14 hour cholecystogram and absence of clinical evidence of an inflammatory process may lead one to suspect but not diagnose a dyskinesia. In this paper we have desired only to emphasize that the possibility of the occurrence of biliary dyskinesia should be borne in mind and requires consideration in the etiologic analysis, diagnosis and therapy of biliary tract diseases.

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PROLIFERATIVE AND EXUDATIVE TUBERCULOSIS WITH REFERENCE TO THEIR RELATIONSHIP TO THE VARIOUS FRACTIONS DERIVED FROM THE TUBERCLE BACILLUS '

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OUR conception of tuberculosis has been subject to vast changes since Villemin proved the transmissibility of the disease and Koch revealed the cause of infection

The pathology of tuberculosis received a clarifying and purifying touch when the discovery of the bacillus showed the unity of all tuberculous processes, and again, when Koch showed that sensitization of tissue cells plays a part in every infection. When the meaning of these two important facts was comprehended we were ready to define the pathologic changes which take place at the site of infection as the reaction of the tissues to the presence of the tubercle bacillus and bacillary products, and to view the reaction of the tissues of previously infected individuals, on again coming in contact with bacilli or bacillary substances, as shown in the phenomena attending subsequent invasion and in the tuberculin tests, as being evidence of a specific defensive mechanism.

The primary reaction in first infection is similar to the reaction of tissues to any foreign substance, but this changes and takes on aspects of specific opposition to the invading living organism as soon as sufficient bacillary substance has gained access to the circulation to sensitize the body cells. Thereafter the more simple reaction of first infection assumes a greater complexity because the entire organism has become prepared in a specific way to meet reinfection and to cope with whatever injurious substances are produced as a result of the growth and destruction of invading bacilli.

The anatomic pathology of tuberculosis consists of the changes in the tissues which are produced when infecting bacilli or bacillary products come in contact with body cells sensitized by bacilli and their products. The clinical expression of tuberculosis consists not only of the changes which are caused by the pathologic structure itself but also of reflex and toxic effects which are expressed in various tissues and organs, disturbing their smooth working and causing departures from physiologic action. It is evident that these expressions may be either local or general.

The difference in reaction of different individuals to tuberculous infection has led to certain groupings of cases according to the predominant characteristics noted. If it were possible for us to know the particular

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factors which determine these major differences, we would thereby greatly increase our understanding of the disease

Even Sydenham and Morton, clinicians of the seventeenth century, recognized an arbitrary classification of tuberculosis into "early," "moderately advanced," and "far advanced" This was based largely on symptomatology and on the recognition of the fact that those with few, mild symptoms were curable and those with serious symptoms were seriously ill and for the most part incurable

Later a classification, using the same terms, was proposed by Turban, which with modifications, is still followed in many countries of the world This classification at first depended on anatomical extent only, but later was modified in the United States by Rathbun's suggestion of adding to it the severity of symptoms, and later by Brown and Heise's suggestion of adding the knowledge gained by the roentgen-ray

These classifications have rendered a great service to tuberculosis, mainly by requiring physicians to appreciate that the smaller the lesion, other things being equal, the more curable the patient, and further by stimulating physicians to develop skill in determining early lesions They have, however, added little to our clinicopathologic conception of the disease

A real understanding of tuberculosis and the ability to predict what course a given infection will take depends upon facts which are more fundamental, facts of an immunologic nature which, if they were known to us, would be sufficient to explain many of the mysteries which at the present time surround the disease

The reaction between the tissues and the bacillus throughout the course of tuberculosis is a combination of cell proliferation and exudation with or without tissue destruction The predominating reaction in different lesions has been used as a basis for classifying them into proliferative or fibroid, exudative and caseopneumonic Miliary tuberculosis is usually classified separately, although it may be predominantly proliferative in one case and predominantly exudative in another

While these reactions are not distinctive and separate, but go hand in hand in the same lesion, yet one or the other predominates sufficiently often to show that a different combination of forces is responsible for the different reactions Anything that will enable us to explain these differences will clarify our knowledge and help us to understand better the specific protective mechanism which the body brings into play when it combats tuberculous infection We must bear in mind that these reactions are a part of the patient's defensive immunity mechanism, or at least are determined by it

What reaction will take place in the tissues in the presence of invading organisms is determined primarily by the tissues themselves and secondarily by the numbers and virulence of the invading organisms That heredity is a factor of great importance is conceded, and that the reaction of the tissues is greatly modified by environment, both internal and external, is likewise recognized On the part of the bacillus, we have two important factors—

numbers and virulence These four factors are the most prominent forces so far as we know in determining the nature of a tuberculous infection

If we now turn to the bacillus we find that, under the direction of the National Research Council, Anderson and his coworkers have separated it into several distinct fractions, and that the effects of these various components on the tissues have been studied experimentally by Sabin, Doane, Cunningham, Long, Seibert, and their coworkers, with the result that certain reactions in the tissues may be more or less accurately assigned to definite bacillary substances

These are among the most important studies that have been made in tuberculosis in recent years, because they give us a basis for understanding the individual reactions of the body against the disease

The following fundamental reactions have now been assigned to the different components of the bacillus by these workers The lipid portion of the bacillus is the cause of the formation of the tubercle The phosphatide constituent seems to possess the simple property of stimulating monocytes and young connective tissue cells to the formation of epithelioid cells and giant cells The waxes cause proliferation of fibroblasts, and the acetone soluble fat induces proliferation of all connective tissue cells and the cells of blood vessels, and is responsible for hemorrhage The polysaccharide is toxic for leukocytes and according to White exerts a damaging influence on the adrenals The protein is responsible for fever, causes proliferation of plasma cells, produces sensitization of the body cells and calls out the allergic reaction later

The lipoids seem to have most to do with the building up of a structural defense while the proteins are more intimately connected with the physiologic protection of the body

While our knowledge is not sufficiently advanced to enable us to discuss the various pathologic changes in their exact relationship to this experimental work, yet we undoubtedly can make certain comparisons which are helpful

Since the two outstanding tissue reactions in tuberculosis are the proliferation of cells, on the one hand, and the exudative reaction of allergy on the other, and since the former has been more or less definitely assigned to the lipoids and the latter to the protein fractions of the bacillus, it might be well for us as clinicians to accustom ourselves to think in terms of these reactions It would seem fair to assume that the lipoids protect the body by holding the bacilli fixed in the tissues, and there is also a possibility that these cells afford a certain protection to the bacilli which they imprison The proteins interfere with the migration of bacilli by causing inflammation and exudation in the tissues which surround them, and if the numbers and virulence of the bacilli are great the reaction may be sufficient to destroy the tissue and eliminate the bacilli en masse The reaction to the protein elements further opposes multiplication of bacilli by increasing phagocytosis

and stimulating other defensive mechanisms of the body which encompass their destruction more rapidly and more efficiently

Now if we examine into the nature of preponderantly proliferative tuberculosis, we note first that it is comparatively mild, and its chief characteristic is new tissue formation. It may extend until wide areas of fibrous tissue are formed before it makes its presence felt by symptoms. It is usually brought to the patient's attention by metastases taking place in some other portion of the lung or in some other organ, or by the process taking upon itself exudative and not infrequently destructive characteristics.

The primary mildness is indicative of a relative absence of physiologic disturbance of the patient, and suggests an infection produced by few bacilli with relatively low virulence which fails to stimulate adequate specific defense. The infection fails to furnish sufficient bacillary protein or to pour toxins into the circulation in sufficient quantities to produce symptoms, and yet regardless of this mildness the tissues are unable to prevent the bacilli from spreading. We must assume, therefore, that there are other factors which require explanation. It would seem that some protection must be present to shield the bacilli from destruction, for they continue to spread regardless of their low numbers and low virulence, or it may be that some factor necessary to encompass their destruction is wanting.

In this connection it will be remembered that Sabin has suggested that the monocytes which are precursors of the epithelioid cells exert a protective influence on bacilli. So the bacilli may not be destroyed, even though they are few in number and low in virulence, consequently they may fail to set free in sufficient quantities the tuberculo-protein which is necessary to build up the patient's physiologic protective mechanism (immunity) to the point of efficiency, although they do set it free in sufficient quantity to sensitize the body cells.

Sooner or later, however, this structural protection, if we may so speak of it, fails, bacilli develop in larger numbers, and through their growth and destruction larger quantities of bacillary protein are liberated which now call forth allergic phenomena and cause the widespread, mild, proliferative lesion to take on exudative characteristics with or without destruction of tissue. When this occurs the allergic reaction may be coextensive with the unhealed lesion which is not infrequently coextensive with the proliferative process, but as a rule, for some time the exudative phenomena are less marked than those found in primarily preponderantly exudative lesions. This indicates that regardless of the minimal amount of bacillary protein which had escaped from the proliferative lesion, sufficient had gained access to the body cells to cause at first sensitization and later a certain amount of desensitization. The chief allergic reaction and the principal destructive phenomena are usually confined to limited areas, it may be a single area at first which may proceed to cavitation. Later, however, when the allergic process becomes more extensive and more severe, multiple small cavities often appear in the midst of the proliferative process.

The supervention of exudative phenomena on a proliferative background probably results whenever the numbers of extensions of the disease become so many at any one time, or whenever they are caused by so large a number of bacilli that local destruction of tissue results and the total amount of bacillary protein set free into the tissues becomes sufficiently great to produce a widespread allergic reaction with or without increased tissue destruction. It would seem then that our best conception of preponderantly proliferative tuberculosis is that it is primarily more a reaction of the tissues to bacilli as foreign bodies than to them as living, multiplying microorganisms which stimulate the body functions to their own destruction, consequently an infection in which structural defense predominates over physiologic defense. Whether this is for the most part due to the cellular protection afforded to the bacilli by the newly formed tissue or to the fact of a failure to set free sufficient amounts of immunizing protein and whatever other substances are necessary to create an efficient immunity is not clear. That bacillary protein may be lacking in these lesions is suggested by the fact that if the course is progressive, the effects of large quantities of bacilli and bacillary protein sooner or later become evident, and the lesion takes on exudative characteristics similar to those of the preponderantly exudative type, and further by the fact that the proliferative lesion may be stimulated to allergic response and healing by bacillary protein as found in tuberculin.

While preponderantly proliferative tuberculosis is mild in degree and usually consistent with long life, it does not heal readily. It is much more difficult to secure a satisfactory recovery from it than it is from the more acute exudative lesions.

Preponderantly exudative tuberculosis, on the other hand, is more acute. Even the early implantations are often made by large numbers of bacilli and are accompanied by the liberation of large quantities of bacillary substances of which the protein fractions are particularly in evidence. Not infrequently the first intimation of illness is accompanied by acute symptoms of toxemia, rise of temperature, weakness, even prostration, and often cough and expectoration. Examination at this time may reveal a widespread exudation in the tissues, not infrequently with loss of tissue. Here, physiologic reaction predominates over structural defense.

The disease may develop slowly as a result of a succession of small implantations of bacilli, or it may come on acutely as a result of massive dosage. In this connection it must be borne in mind that the term "numbers of bacilli" is not a measured dosage but a relative term depending on the individual and his antecedent dosage, for desensitization takes place as a result of repeated inoculations. So what would be a large dose at the beginning of a disease would probably be small later in its course.

With this form of the disease the patient is more severely ill than with the preponderantly proliferative form. There is more danger of the disease spreading quickly and more danger of tissue destruction. On the other hand, a higher immunity develops. The acuteness of the symptoms is

probably caused largely by the protein fractions of the bacillus which produce a widespread exudation with or without tissue destruction, although destroyed tissue products and other bacillary elements can not be excluded. The same dose of bacilli or bacillary protein which causes the acute symptoms seems to whip up the immunizing mechanism and to desensitize the patient so that he is thereafter enabled to withstand the effects of larger numbers of bacilli and of greater quantities of bacillary protein without reacting so severely. While proliferation goes hand in hand with exudation and destruction, yet it is relatively a minor part of the early stage of preponderantly exudative lesions but a very important part of the healing process.

Preponderantly exudative lesions yield readily to treatment if it is applied at once. The infection is not coextensive with the exudative phenomena, but must be looked upon as being a limited infection with a large local tuberculin reaction which, when it has cleared away, which it will do largely by resolution, will leave a fairly free lung field. Being acute it comes on before the lung has been seriously injured and when its power to make necessary compensation for healing is unimpaired.

FURTHER STUDIES ON GRANULOPENIA WITH A REPORT OF TWELVE CASES¹

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SYNONYMS

WITH the increasing incidence of this disease, it is natural that new terms should be used. The original name was agranulocytosis and the indices usually refer to it under this heading or as agranulocytic angina. Agranulocythemia and hypogranulocytosis are also used—the former as a synonym of agranulocytosis and the latter to mean a leukopenia but not a complete granulopenia. Malignant neutropenia and primary granulocytopenia are used in the same sense as agranulocytosis or complete granulopenia. Primary granulopenia is also used in the sense that the granulopenia does not result from any other disease. Two points need to be distinguished. Complete granulopenia or near complete granulopenia or agranulocytosis is a rare and dangerous disease of the bone marrow. Mild or moderate granulopenia is a very common state of the blood stream and not in itself very dangerous. Complete granulopenia is a disease, leukopenia a mild decrease in the leukocytes. If the terms be limited to the granulocytes, one may distinguish the two conditions as complete and incomplete granulopenia. Partial or total granulopenia are other qualifying adjectives meaning the same thing. We prefer the terms complete and incomplete granulopenia to distinguish the rare disease from the frequent state.

THE MECHANISM OF COMPLETE GRANULOPENIA

To understand the mechanism of the disease is to understand the disease itself with, of course, certain limitations in our present knowledge. The order of events in this mechanism was submitted at length in our first paper¹ and we believe with reasonable evidence of proof. There are five stages of the disease and they follow each other with inevitable and inexorable regularity. First and for some reason, now largely speculative, there is the bone marrow onset. The bone marrow is an organ and its myelocytic function fails. So far as we can see, it makes little difference whether one speaks of this selective myelocytic failure with cessation of the production of the granulocytes as a myelocytic aplasia, myeloblastic dysfunction, cessation of maturation, allergy or what not. It is a selective bone marrow failure with a resultant blood stream granulopenia even to the point of a complete absence of the circulating granulocytes. Secondly, about four days after this bone marrow failure, there is the blood stream onset. The

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change may appear in the blood count in one to two days with gradual lessening of the granulocytes to complete or near complete absence. Thirdly, the clinical onset comes more quickly, usually in 24 to 48 hours with complete granulopenia, weakness, prostration, and fever, rarely early mania and later exhaustion and delirium. Fourthly, the granulocytes protect the tissues with an ever present daily immunity from bacterial invasion. This protection is now lost, and bacterial invasion begins. Therefore, so far as is now known, this is a non-bacterial disease with a bacterial ending. Blood stream infection, tissue necrosis and gangrene, ulceration and hemorrhage follow. This is the stage of sepsis. Fifthly, and lastly, the parting of the ways has come. It is granulocytes or death. There is no mid course. The bone marrow may even resume its myelocytic function, but death may occur from sepsis before maturation proceeds to the appearance of myelocytes and granulocytes in the blood stream. This is the mechanism of complete granulopenia. One may object that this is too mechanistic a conception for a hematological problem, but the facts square with the conception.

RELATIVE FREQUENCY OF MILD GRANULOPENIA AND THE CHRONIC GRANULOPENIC PATIENT

In our second paper we² studied the general subject of granulopenia and made comments illustrating the granulopenic trend on the basis of blood studies on 8,000 private patients. The general conclusions have been confirmed by a similar study made by Mettier and Olsan³ at the University of California Hospital on 10,000 cases between 1920 and 1931, inclusive. A study of our paper and their paper shows the frequency of leukopenia, its trends and its wide implications. In general it may be said that leukopenia is an important factor and probably as important as a leukocytosis.

The granulopenias are classified under 10 different headings of which acute complete granulopenia is only one. A chronic granulopenia is described of which acute granulopenia is probably an extreme degree. One out of every four patients may be expected to have a mild granulopenia. One of two female patients between the ages of 40 and 60 may be expected to show a mild granulopenia. The complaints of weakness, exhaustion and fatigue are twice as frequent in the granulopenic patients as in those with normal white cell counts. There appears to be a definite even if rather vague clinical syndrome that consists mainly of weakness, easy exhaustion and chronic fatigue, a loss of strength with physical inertia associated with a chronic diminution in the number of granulocytes. The severity of these symptoms which are, of course, largely subjective, seems to depend upon the degree of diminution of the granulocytes until with complete absence of the granulocytes such as characterizes an acute complete granulopenia, there is extreme weakness and physical collapse. Mettier and Olsan found 1,167 patients out of 10,000, or 11.67 per cent, with granulopenia. Their figures show 52.4 per cent in females and 47.6 per cent in males. They classified 9.7 per cent of their cases of leukopenia as "benign leukopenia of obscure

origin" The careful and prolonged study of a single leukopenic patient rather than the mass study of many leukopenic patients promises valuable results

Granulopenia whether acute, chronic or recurrent, is regarded as a disease entity in the same sense and as definitely as pernicious anemia is so regarded Granulopenia, when associated with other diseases (usually then called leukopenia) is not rare, and here Fitz-Hugh and Comroe²⁰ well call it "a mere hematological manifestation" of other diseases Among these may be mentioned typhus and typhoid fever, influenza, measles, mumps, dengue fever, certain stages of tuberculosis and syphilis, fulminant sepsis and later stages of extreme anemias It is a common and widespread hematological condition long known and often used as a diagnostic aid A college student with 80 per cent lymphocytes in a total leukocyte count of 1,600 was treated for the disease acute granulopenia, but developed on the fourth day definite signs of typhus fever, and an old man of 77 with only 34 per cent granulocytes in a total count of 2,000 was proved to have an advanced hypochromic anemia A leukopenia with complete or near complete absence of the granulocytes, which constitutes the essence of the disease granulopenia or agranulocytosis, is one thing, and a leukopenia that is a blood sign of a disease of which it is a part, is quite another thing Fine judgment and acumen may be necessary to make the differentiation Sometimes only waiting will solve the problem The point to be emphasized is that a low granulocyte count is not of itself proof of the disease granulopenia

Granulopenia occurs in aplastic anemia Here all three of the elements in the bone marrow are affected, viz, the granulocytic, the erythrocytic and the thrombocytic cells In the disease granulopenia only the myeloblastic tissues are involved Wide variations and gradation occur in the count of the granulocytes in pernicious, aplastic, and hypochromic anemias, and even in the aleukemic states of the various leukemias and particularly the myeloid type In the last great care is necessary, for a leukemic patient may present a leukocyte count of 2,000 or less The majority of these cells may be the blast type of the myeloid series It is easy on account of their relatively small size to call them lymphocytes in error and make the diagnosis of granulopenia At times a myeloid leukemia is so closely imitated by the leukopenia of other diseases, including certain anemias, that one must take all precautions to be sure of the diagnosis Complete granulopenia seems to characterize agranulocytosis alone It is the case of incomplete granulopenia that brings the greater difficulty Of course the clinical signs and symptoms are of great aid

THE WORLD INCIDENCE AND GEOGRAPHIC DISTRIBUTION OF COMPLETE GRANULOPENIA

Our present knowledge of the world distribution of granulopenia is dependent upon reports in the literature The diagnosis of the disease depends upon the study of the blood, and in those areas and countries where

blood studies are the exception rather than the rule, the disease may occur as frequently as in America or Germany and yet be overlooked. Even in America it is reported far more frequently as a rule in those centers where a certain group are particularly interested in the disease, its problems and treatment. Blood studies are requisite for its recognition. There seems no available reason why it should not appear as frequently in England as in other civilized countries and the failure to make systematic blood counts is probably the reason for the paucity of English reports. From the literature to date (and more cases are reported from month to month) there is evidence that it is of world-wide distribution. The facilities for blood studies and for reporting disease are probably more highly developed in Germany and the United States than in other countries, and these two countries so far furnish the majority of reported cases. We have summarized 473 cases in the United States and over 400 in Germany. Reports continue to come in from France and Italy. It has been reported from Japan, China, Dutch East Indies, Russia, Poland, and Syria. Dennis⁴ writes that cases have been seen in Palestine and Egypt, and several cases have been studied by Dr Kleeborg in Jerusalem. So far only six cases are reported from England. Time will finally show its real incidence and distribution.

AGE, RACE, SEX, OCCUPATION AND SOCIAL INCIDENCE

Acute granulopenia may occur at any age from less than a year to more than 80 years of age. The majority of cases occur between 30 and 50 and the average age of the 473 cases reported in the United States is between 40 and 50 years. It is chiefly a disease of middle life so far as reported cases show. This age incidence is an urge to complete and even repeated blood studies in cases of doubtful diagnosis.

So far the disease affects principally the white race. Its frequency in the yellow races is unknown. Further reports are necessary to clear this point. We have not observed a single case in the negro over a period of five years and with an annual admission rate of 75,000 negroes to the Emory University Division of the Atlanta City Hospital. This rarity in negroes seems to be true throughout the continental United States. Further facts are necessary before its final incidence in negroes can be stated. Sick negroes outside hospitals rarely have blood counts and most sick negroes never enter a hospital. In the eight cases listed below in negroes, the clinical onset in nearly all of them followed the administration of arsphenamine. The following table gives the present trend of race and sex incidence.

TABLE I

| | |
|-------------------------------------|-----|
| Number of cases in the U. S. | 473 |
| Number of cases in the white race | 442 |
| Number of cases in the colored race | 8 |
| Race not stated | 23 |
| Number of cases in males | 161 |
| Number of cases in females | 310 |
| Sex not stated | 2 |

Thus far the disease is reported in the ratio of nearly two females to one male, or actually of 310 females and 161 males. This ratio is very difficult to interpret and particularly in regard to etiology. Probably one-third to one-half of the very sick people in this country do not have the interpretative benefit of a blood count and further studies may change this ratio. Of our 12 cases, eight were women and four, strong men.

A case in point was that of a school teacher that one of us (S. R. R.) was called in to see in 1927. She had already previously been seen by two physicians, but although the patient was very ill and had become unconscious, no blood examination had been made. Had she been a nurse, she would doubtless have been taken to the hospital at the beginning of her illness and the diagnosis been made promptly. As it was, the disease was overlooked, and the diagnosis made of streptococcic throat was in error. A majority of people who die in the world never have had the benefit of a blood examination. We do not know how many people have complete granulopenia and must resist the temptation to leap to a speedy conclusion from a very limited experience over a very short period of time.

SOCIAL INCIDENCE

It is apparent thus far that a majority of cases reported appear among those in the middle and upper classes, in the higher economic and cultural levels. On the other hand, the great majority of people on the lower economic levels postpone treatment, or may not see a physician until necrosis of the throat is so far advanced as to permit a glib diagnosis of malignant sore throat, or have no hospital facilities and no opportunity to receive a correct diagnosis. More facts are necessary for a conclusion involving social incidence. In American medicine one does well to remember that there are 125 million people in the United States and that many millions of them do not have the benefit of any modern medical facilities, much less adequate medical care.

OCCUPATION

The following table shows the occupation of 250 of the 473 cases in the United States. In 223 cases data as to occupation are not furnished. Conclusions, or even intimations, from such a table are scarcely warranted. However, it is apparent that to date the disease has appeared most frequently in housewives and in persons falling into the medical group.

TABLE II

| | |
|--------------------------------|--------|
| Housewives | 102 |
| Physicians | 22 |
| Nurses | 17 |
| Hospital employees | 4 |
| Medical students | 3 |
| Laboratory technicians | 1 |
| Relatives of physicians | 11 |
| School teachers | 2 |
| Farmers | 5 |
| Business men—all types | 10 |
| Sixty other occupations (each) | 1 or 2 |

Many have noted this predilection of the disease for physicians and their families, nurses, medical students, technicians and others of the medical group. It has been commented upon in the papers of Kracke^{17, 21} and by Stellhorn and Amolsch.⁷ Among Harkins'⁵ eight cases there were a doctor, a medical student and a nurse. In Madison and Squier's⁶ series of 14 cases there were five in the medical group counting the wives of two physicians, and the authors write, "In this group (of cases) as in the disease at large, there seems to be a remarkable relation to the medical and allied professions." This statement undoubtedly applies to the group of cases they reported but probably does not apply, in the same proportion, to "the disease at large." In our group of 12 cases, for example, there were only two, a physician and a nurse, from the medical group. It is true that of the males reported 13.6 per cent are physicians and of the females 5.4 per cent are nurses. A factor of some importance in determining this rather large percentage of the medical group is that sick doctors and nurses go more quickly to hospital in our experience than do others and more quickly receive the benefit of repeated laboratory examinations and consultations. In the medical group so rare a disease or so baffling a case would probably receive the most thorough study and the quickest diagnosis.

Comment is certainly justified upon the fact that the disease has occurred most frequently in women and especially among those classified as housewives, of the eight women in our series seven were in this occupation, if it may be so called. To date the data from reported cases allow of no difference of opinion on these points.

PRESENT IDEAS OF ETIOLOGY

The cause of the disease is unknown. From the present evidence, there seems to be no single etiological factor that fits every case, nor has it been proved that any of the possible causes that have been suggested are responsible for the disease. With a new disease one fishes quickly in the pond of cause and effect in the hope that the prize fish of etiology may soon swallow bait, hook and sinker. All these excursions ultimately will result in the discovery and proof of the etiology. One steps very carefully here. Coincidence does not necessarily mean proof. Different points of view, clinical observations and experiments with animals all produce positive or negative evidence, and all are valuable. The various suggestions as to etiology offered by students of the disease are summarized in the following table.

TABLE III

- 1 Specific bacterial etiology nothing conclusive discovered
- 2 Abnormal menstrual states
- 3 Certain anemias, aplastic, pernicious and secondary
- 4 After leukopenic diseases, as influenza
- 5 Certain drugs, as arsphenamine, amidopyrine and benzene ring compounds
- 6 Exhaustive states, induced by toil, worry, and mental effort
- 7 Certain senile states in asthenic women

1 *Bacteria* Since Lovett⁸ reported the first case of this disease in the United States many studies have been made in an effort to incriminate a specific bacterium. She attempted to show that the *Bacillus pyocyaneus*, which she found in the oral ulcers of her patient, was responsible, but without success. Since that time much experimental work has been done with bacteria in an effort to reproduce the disease in laboratory animals but it has been uniformly unsuccessful. Many of the bacteria involved have been the various streptococci, the *Bacillus pyocyaneus*, bacillus of hog cholera, dead and living typhoid bacilli, Vincent's organisms, etc. Many writers have stated that various degrees of granulopenia have been produced in laboratory animals with these organisms but apparently they did not take into account the fact that transient and temporarily severe leukopenic states can be produced with nearly any and all bacteria, dead or living. A significant contribution is that of Dennis,⁹ who was able to produce a prolonged granulopenia by the introduction of *Streptococcus viridans* in parchment capsules into the peritoneal cavity of rabbits. One of us (R. R. K.) has repeated, in so far as possible, this work and is unable to confirm the results of Dennis.

There seems no evidence that there is a specific bacterial etiology. Positive blood cultures were obtained in about 20 per cent of the total number of cases, they were positive in 70 per cent of the cases on whom cultures were taken. The streptococci were by far the most frequent invaders. There were 74 positive cultures and 395 cases in which cultures were either negative, or not stated as taken. The data in table 4 illustrate this point in detail.

There is no more reason to suspect a bacterium to be the cause of this disease than to suspect a specific bacterium to be the cause of aplastic anemia. On the other hand, as we¹ have shown in our first paper, the blood stream infection is probably secondary to the leukopenic state. One must keep the horse of acute granulopenia with the loss of immunity to bacterial invasion ahead of the cart of the secondary bacterial invasion. This explains why so many different bacteria are recovered in blood cultures. This explains why the usual surgical treatment of the secondary infection and necrosis is so unavailing. This explains in terms of treatment why this secondary infection, particularly with pus producing bacteria, is the chief therapeutic hope of the patient, because it is nature's method of quickly arousing a leukocytosis.

2 Hubble¹⁰ suggests that glandular dysfunction may play a rôle in producing the disease and suggests that bone marrow depression may be caused by a pituitary basophilic insufficiency or granulopenia by cortical adrenal dysfunction. Corey and Britton¹¹ observed an agranulopenic syndrome in adrenalectomized cats and Thompson¹² believes that the disorder may be associated in some way with the glandular changes of menstruation. Thompson's studies are worthy of serious consideration. Our case 8 was afflicted with menorrhagia as well as great toil and worry. The temptation may be to dismiss these suggestions as too speculative.

TABLE IV
Blood Stream Infection in Granulopenia

| Organism | Number of Cases |
|--|-----------------|
| <i>Streptococcus hemolyticus</i> | 8 |
| <i>Streptococcus viridans</i> | 15 |
| <i>Streptococcus</i> (type undetermined) | 9 |
| <i>Staphylococcus albus</i> | 3 |
| <i>Staphylococcus aureus</i> | 4 |
| <i>Bacillus Friedlander</i> | 4 |
| <i>Pneumococcus</i> , type 2 | 3 |
| <i>Pneumococcus</i> , type 3 | 1 |
| <i>Pneumococcus</i> , type 4 | 2 |
| <i>Pneumococcus</i> , type undetermined | 2 |
| <i>Diplococcus</i> (undetermined) | 4 |
| <i>Bacillus pyocyaneus</i> | 3 |
| <i>Bacillus paratyphosus B</i> | 1 |
| <i>Bacillus coli</i> | 3 |
| <i>Bacillus proteus</i> | 1 |
| <i>Streptothrix</i> | 3 |
| <i>Streptococcus</i> with other bacteria | 9 |
| Fusiform bacillus (Gram negative) | 1 |
| Estivo-autumnal parasite | 1 |
| Various cocci | 3 |
| <i>Staphylococcus</i> (undetermined) | 1 |
| <i>Diphtheria bacillus</i> | 1 |
| Vincent's organisms | 1 |
| Typhoid bacillus | 1 |
| <i>Bacillus</i> (undetermined) | 1 |
| Total number of positive cultures | 74 |
| Negative, or not stated | 395 |

3 The possible relation to certain blood diseases is discussed under the heading of "Relation to Other Diseases." Suffice it to say here that other anemias may depress the myelocytic function of the marrow with a resulting granulopenia. Such a granulopenia may thus invite bacterial invasion and hasten death. We have seen this in a case of acute lymphatic leukemia. It is common in aplastic anemia to see a granulopenia.

4 Cases 2, 5 and 7 of our series followed influenza in an influenza epidemic. We have before pointed out the great weakness and prostration in the acute infections characterized by granulopenia.

5 There has been much recent discussion following the suggestion that arsphenamine, amidopyrine and benzene ring compounds may cause the disease. Much of the discussion about the relative frequency of the disease in the medical group of occupations, i.e., doctors, nurses, technicians, etc., finds its point here. The granulopenic state following arsphenamine administration in certain cases has long been recognized. The frequency of granulopenia in those treated with gold salts for tuberculosis has been observed by several French writers^{13, 14, 15}. The possible rôle of certain coal tar drugs in the production of the disease has been stressed by Kracke^{16, 17}. Madison and Squier⁶ have presented evidence that all of their cases were given drugs of this class preceding the clinical onset. Chief among these drugs under suspicion at this time is amidopyrine alone or in combination

with a barbiturate. On the other hand, Thompson¹⁸ states that he has carefully investigated the histories of his 46 cases of granulopenia and that there is no evidence to incriminate either amidopyrine or the barbiturates. Circumstantial evidence continues to accumulate that amidopyrine in certain cases has power to depress the myelocytic function of the bone marrow.²³ This is certainly not true, however, of all persons to whom amidopyrine is administered. These differences in myelocytic response to amidopyrine intimate therefore that the myelocytic function of the bone marrow varies in the degree of its sensitivity. Pepper¹⁹ refers to the allergic predisposition of individuals who have granulopenia. We have not confirmed his suggestion in our series. Perhaps one who has granulopenia may have a weakened or inferior marrow which may be hypersensitive to allergic influences, but this would be very difficult of proof.

EXHAUSTIVE STATES

It is curious that cases 1, 2, 3, 4, 6, and 10 of our 12 cases, and another case reserved for a later report, and not included in this series, were lean, pale, asthenic women of little reserve. Each of them lived on a lower level of strength and activity than normal and one could well call them frail, exhausted women. Their families spoke of them as "lacking strength, complaining of weakness and unable to stand much strain." Most of them were of middle age or older and physically below par with a hemoglobin ranging from 60 to 70 before granulopenia developed. One can only speculate here that the bone marrow, viewed as an organ, may become selectively exhausted or disturbed to such a degree that normal function is impossible. There is selective failure of the myelocytic function of the bone marrow. We have seen erythrocytic failure repeatedly in senile hypochromic anemia. Cases 8 and 11 of our series had their attacks after prolonged toil, loss of sleep and great worry and each of them had been warned long before the attack that she could not continue to work so hard. Women of a certain asthenic type and women of great toil form a suggestive group.

THE HEMORRHAGIC TREND IN COMPLETE GRANULOPENIA

In the reports of the postmortem examinations one finds recurring references to hemorrhages both dermal and visceral. A study of this hemorrhagic tendency affords material for a good paper. We have seen during the course of the disease petechiae on the conjunctiva, the oral and rectal mucosa, the skin, then larger purpuric areas even to a massive purpuric area involving one-third the trunk. Bleeding may occur from the nose, throat, alimentary tract, urinary tract, uterus and vagina. Such bleeding is as a rule small in amount. We have seen at postmortem examination petechial and larger hemorrhages in the lungs, subpleural hemorrhages, and petechiae in the epicardium, endocardium, stomach and intestines.²² In one case

there was an acute hemorrhagic splenitis. Sepsis may be an important factor in the production of these hemorrhages. The platelets may show a marked decrease. No hemorrhages may be seen during life and yet necropsy may reveal many. It is rare to see a case in which there is not some manifestation of this hemorrhagic trend. With large purpuric areas the superficial likeness to purpura may confuse the diagnosis and we have seen this mistake made once. This tendency to hemorrhage probably arises from a bone marrow dysfunction involving the megakaryocytes and a decrease in platelet formation. Complete granulopenia may masquerade with a purpuric front. Careful blood studies tell the story. Purpura hemorrhagica may be cured with transfusion or splenectomy, but not a complete granulopenia.

REPORT OF TWELVE CASES

The following 12 cases, only one of which has been previously reported, illustrate definite points in the disease. We have another case for a future report because there have been two attacks and we have followed the blood carefully over a period of two years.

The more one studies these cases and the hemograms, the more the evidence points to the reappearance of granulocytes in the blood stream as the one chief purpose of treatment and the one hope of recovery. Table 5 gives a condensed summary of these 12 cases, and the history of each case more in detail follows.

CASE REPORTS

Case 1 Mrs W W F, aged 46, a patient of Dr W F Shallenberger, had five cystoscopic examinations during 1928. Otherwise she appeared well. Four days after the last examination on November 16, 1928, she became extremely weak, an unexplained fever developed and she died on the third day with a leukocyte count of 400 cells.

Case 2 Mrs L Z R, aged 72, an asthenic woman with a chronic secondary anemia, developed on March 12, 1929 fever, prostration, a red, edematous and quickly necrotic throat, and a white cell count of 2,000 with no granulocytes. She was unconscious and delirious, with a profuse diarrhea. Concurrent with the development of embolic abscesses in the skin and deep abscesses in the muscle of the calf, she showed a widespread infection with the *Streptococcus hemolyticus* in the blood stream, skin and muscle abscesses. Despite the previous absence of granulocytes for days, myelocytes and juvenile forms began to appear in the blood stream after the abscesses developed, and in eight days she had a leukocyte count of 41,000 with 84 per cent granulocytes. She had been convalescent for 65 days and appeared to be in better health than formerly, when the white cell count quickly dropped to 400 with complete absence of granulocytes and she died on the fourth day of the second attack.

This case has previously been reported in detail, and affords proof that the bone marrow in severe acute complete granulopenia may not be irreparably damaged, but with time and stimulation of myelocytic activity may still be capable of normal function. We believe that the stimulation in this

TABLE V

| Case | Sex | Race | Age | Occupation | W B C | R B C | Platelets | Hemor- rhage | Bone Marrow Regeneration* | Terminal Infection | Result |
|------|-----|------|-----|--------------|-------|-----------|-----------|-----------------|------------------------------|-----------------------|-----------------|
| 1 | F | W | 46 | H W | 400 | | | None | Died 1st attack | None | Died |
| 2** | F | W | 72 | Ret H W | 400 | 3,500,000 | Normal | None | Yes | Strep hemo | Died 2nd attack |
| 3 | F | W | 34 | H W | 450 | 4,000,000 | Normal | None | No | No | Died |
| 4** | F | W | 44 | H W | 470 | 5,200,000 | Normal | None | Yes | No | Died 3rd attack |
| 5 | M | W | 50 | Physician | 400 | 3,160,000 | Normal | None | No | Broncho- pneumonia | Died |
| 6 | F | W | 35 | H W | 400 | 2,800,000 | Decreased | Yes | No | No | Died |
| 7 | M | W | 64 | Police chief | 950 | 3,700,000 | Normal | No | No | No | Died |
| 8 | F | W | 48 | Librarian | 450 | 4,300,000 | Normal | No | No | Strep hemo | Died |
| 9 | M | W | 50 | Mill-worker | 450 | 5,600,000 | Normal | No | Yes | No | Died 2nd attack |
| 10 | F | W | 38 | H W | 450 | 4,800,000 | Normal | No | Yes | No | Recovered |
| 11 | F | W | 26 | Nurse | 300 | 4,900,000 | Normal | No | No | Yes | Died |
| 12 | M | W | 42 | Business man | 200 | 4,300,000 | Normal | No | No | No | Died |

* Bone marrow regeneration refers to development of leukocytosis after granulopenic attack

** Case previously reported in detail

case was due to the infection with *Streptococcus hemolyticus*. This case also proves that the fall and absence of the granulocytes precedes by one or more days the clinical onset of the disease.

Case 3 Mrs R G, aged 34, had influenza in early March of 1931. She had been weak and unable to resume her usual activity. She had run a slight post-influenzal temperature and on April 7 was confined to her bed on account of weakness and fever. The leukocyte count was only 2,000 and granulocytes were absent. The course of the disease was septic and stormy and death occurred on the seventh day with a total white count of 450, all lymphocytes. Postmortem examination showed a hypoplastic bone marrow, patched yellow and red, with numerous subpleural and subperitoneal petechial hemorrhages.

This case illustrates severe acute complete granulopenia, a normal platelet count, no clinical evidence of hemorrhage and yet multiple small hemorrhages at necropsy.

Case 4 Mrs F P S was an asthenic woman who had long suffered with methemoglobinemia and its characteristic slate blue color. For some weeks she had complained of weakness and fever and had presented evidence of mild sepsis. Her leukocyte count was 900 with no granulocytes. The count gradually fell to 470 and rose during the next 25 days to 5100 leukocytes with 80 per cent granulocytes. This attack began on May 13, 1930. On June 30, 1930, 48 days later, she developed a pleurisy with effusion, with a leukocyte count of only 2500. On July 16 her leukocyte count had risen to 4000. A third attack of granulopenia occurred on November 22, 1930 with a total leukocyte count of only 200, entire absence of granulocytes, and death the next day, November 23, 1930.

This case illustrates again that the bone marrow is capable of regeneration within limits. The woman recovered from two attacks only to die in the third. It also shows the association of methemoglobinemia with complete granulopenia. She gave a history of having taken phenacetin for the three previous years and this was probably the cause of the methemoglobinemia.

Case 5 Dr C E S, physician, 50 years of age, was taken acutely ill on April 9, 1931, with a leukocyte count of 1450, and no granulocytes. He had done a heavy practice for the preceding six months by day and night and in the middle of March had suffered a rather severe attack of influenza. He ran a stormy septic course in his final illness with a gradual fall in the granulocytes and died on the fifth day of a terminal bronchopneumonia with a total white count of only 400. There was necrosis and edema of the throat. Purpuric areas developed over the elbows. During a transfusion, blood was seen to pass outward through the wall of the median basilic vein and infiltrate the surrounding tissues. Purpuric areas appeared at once on the adjacent skin. The blood pressure was 125 systolic and 100 diastolic. His liver and spleen both were palpable. Hiccoughs were frequent. Profuse diarrhea and emesis occurred, and moderate delirium alternating with periods of orientation were noted. Necropsy was refused.

This case illustrates the damage done to at least one vein. He probably had many hemorrhages throughout the body. It is noteworthy that the case followed influenza, and the influenza followed a period of great exhaustion.

Case 6 Mrs M N, aged 35, fell ill on April 18, 1931 with a necrosis of the throat following acute follicular tonsillitis which had lasted for 18 days. For the 10 days previous to April 18 and the onset of the necrosis, her temperature had averaged 103°. She was prostrated with weakness. Her leukocyte count was 2100 with 2 per cent granulocytes. There was a stormy course with sepsis and hemorrhages and she died on the eighth day with a total white count of 400 and no granulocytes. The necropsy showed many hemorrhages in the skin, subcutaneous tissues and viscera.

This case illustrates the hemorrhagic trend associated with complete granulopenia and its secondary sepsis. The platelets were only slightly decreased. Sepsis followed the granulopenia. The bone marrow did not respond to the stimulation of the sepsis.

Case 7 Mr M D G, aged 64, chief of police, had been in excellent health for the past year. One week before his acute attack of granulopenia he had influenza. On March 7, 1930 he had fever and was weak and felt badly. On March 8, he had a chill and his throat was red. On March 9, he had a total leukocyte count of 2260 with no granulocytes. He died 48 hours later with a count of 950. There was no evidence of necrosis.

This case illustrates that an acute complete granulopenia may come like a storm, run a rapid course and cause death in four days with no evidence of necrosis. He had no visible evidence of infection at any time save the redness of the throat. There was hardly time for sepsis to develop. The cause of death was evidently the mere absence of the granulocytes.

Case 8 Miss M L, librarian, 48 years of age. For the past three months she had nursed both of her aged parents, done all the house work including the cooking and washing, worried much, was in the menopause and had suffered two moderate uterine hemorrhages. On August 12, 1934, she began to feel ill and noticed that her throat was red and slightly sore. She became weaker, with increasing redness of the throat and more and more prostration, and on August 15, 1932, a hemogram showed a total leukocyte count of only 950, with no granulocytes. She showed the characteristic physical prostration, and mental dullness varying from delirium to coma. She died on August 20 with a leukocyte count of 450, not a granulocyte was seen during the entire course of her illness. A *Streptococcus hemolyticus* was isolated from the blood stream. Necrosis and edema of the throat were extreme. Necropsy results were unimportant except that a gas bacillus was cultured from the necropsy blood.

This case illustrates acute complete granulopenia following a long period of exhaustion, and associated with two previous moderate uterine hemorrhages.

Case 9 Mr F S, mill worker, 50 years of age, was admitted to the hospital on February 23, 1931, complaining of pain in the lower left quadrant of the abdomen of two months' duration. His blood count showed 8500 leukocytes with 60 per cent granulocytes. A diarrhea was present, and examination revealed multiple superficial ulcers in the sigmoid and rectum. His liver and spleen were palpable. On April 2 his leukocyte count had fallen to 1500 with only 2 per cent granulocytes. Sepsis developed with necrosis in the mouth and throat. A sternal puncture was done and the examination of the bone marrow revealed marked hyperplasia and not aplasia. Four days later the total leukocyte count had quickly risen to 22,000 with 70 per cent

granulocytes. The patient was, of course, much improved. The leukocyte count continued normal or above until May 29, when it quickly fell to 600 leukocytes with no granulocytes and the patient died the next day. During the first attack there was also necrosis at the anal margin.

This case illustrates two attacks of granulopenia. The patient recovered from the first attack because the myelocytic function of the bone marrow was resumed. His sternal puncture and bone marrow study were made during the first attack, but at a time when the marrow had resumed its activity and become hyperplastic. This is proved by the fact that myeloblasts, promyelocytes and myelocytes were found in the bone marrow smear at a time when the peripheral cell count was only 450 with no granulocytes. The condition of the bone marrow resulted four days later in a total leukocyte count of 22,000. At necropsy following death in the second attack, the bone marrow was markedly aplastic. The patient had died because the bone marrow in the second attack did not resume its myelocytic function, and granulocytes did not appear in the blood stream.

Case 10 Mrs. A. L. K., aged 38, a patient of Dr. Trimble Johnson, whom we saw in consultation, entered the Emory University Hospital on March 30, 1933, complaining of fatigue and sore throat of several years' duration. She was an asthenic woman with a reddened throat and small pharyngeal ulcers. The total leukocyte count was 950, and no granulocytes were seen. The leukocyte count remained at this level for three days, during which she ran a septic temperature and quickly developed a deep necrosis of the left foot and the lower one-third of the leg. In five days the leukocyte count had risen to 30,250 with a predominance of granulocytes and myelocytes. During the next 30 days the leukocyte count gradually fell to normal and the foot and leg gradually healed. There was much sloughing of the necrotic area. She is still well, one year after recovery from the first attack.

It seems to us that the chief factor in her treatment was the development of the extensive necrosis and gangrene of the left foot with its coincident stimulation of the bone marrow. The organisms isolated from the necrotic area were all pyogenic in type. This necrosis and these pyogenic bacteria confirm our conception that infection is secondary to the granulopenia and that the patient's chief chance of recovery is afforded through the secondary infection itself.

Case 11 Miss S. K., white female, aged 26, a nurse, patient of Dr. C. W. Strickler and Dr. Lon W. Grove, whom we saw in consultation, had been working very hard for the past several months. She was admitted to the Emory University Hospital September 9, 1933, complaining of weakness, general aching, fever and chill occurring the previous day. Physical examination was negative except that she had had a superficial skin eruption of the fingers of the right hand. The total leukocyte count was 2,000 with 4 per cent granulocytes. She grew rapidly worse, sepsis developing with high fever, and necrosis and edema of the right hand. Death occurred on the seventh day with a total leukocyte count of 300, with no granulocytes. The blood cultures were negative.

This is the second case we have seen which had a chill. There had been a mild vesicular eruption of the right hand with superficial ulceration, the

necrosis took hold here rapidly and deeply, and the edema extended quickly as high as the right axilla. Even with such inflammation and necrosis the bone marrow did not respond to its stimulation.

Case 12 Mr J P M, aged 42, executive, patient of Dr J P Tye of Albany, Ga, entered the hospital on January 16, 1934 with marked weakness, physical prostration and a red and edematous throat. One year previously his physician had told him that he had a low white cell count. During the past year he had suffered with multiple arthritis. For eight days he ran a stormy septic course, with increasing fever and progressive weakness. The total leukocyte count dropped to 400 with no granulocytes. Death occurred on the eighth day.

Here was an instance of the disease attacking a strong, though slightly obese, individual, a man of great muscular development, a former football star, who had lived a vigorous outdoor life up to his last illness, with the exception of the limitations imposed by the moderate multiple arthritis. Two of our cases were of this type and both died. Here was acute complete granulopenia that ran a stormy course with complete myelocytic failure.

THE CAUSE OF DEATH

Nature has certain requirements for the existence of the individual. Oxygen, for example, is necessary for life. There is so little reserve of oxygen in the tissues and the need for it is so urgent and imperative, that one can hold one's breath only for about a minute or less. Similarly, the granulocytes seem necessary for the existence of the individual. Complete granulopenia seems to be the first disease that has almost dramatically forced this fact to our attention. One may live with 2,000 or 200,000 granulocytes but without them there can be no life. As a rule, in proportion as the granulocytes fall below the normal level, so does robust living lessen. Nature appears to have given the granulocytes a wider amplitude of daily variation than any other cell of the blood. The count may dip and rise under many influences. Normally they vary with the daily ebb and flow, but in time of need they rise with exercise, inflammation, excitement and even food. The granulocyte may be regarded as a highly specialized cell with multiple functions. These cells and these functions are necessary for life.

1 One function seems to be to confer upon the tissues of the normal individual an ever present daily immunity to bacterial invasion. In complete granulopenia this immunity is lost, and one to four days after the granulocytes disappear from the blood stream, bacterial invasion usually proceeds rapidly. This invasion is stopped and the living bacteria in the blood stream and tissues cease their activity and die, or are eliminated, only by the reappearance of granulocytes in the blood stream. Without granulocytes there is sepsis, and with sepsis there is death unless the granulocytes reappear.

2 It seems that the presence of the granulocytes is necessary to the individual for the maintenance of his daily normal strength. In complete

granulopenia, even before bacterial invasion has taken place, we have repeatedly seen the quick phases of fatigue, exhaustion, prostration and even collapse. We have seen this progressive loss of strength in our first case and consistently in all the subsequent cases. It is bedside observation with proof. The longer the granulocytes are absent, the greater the prostration. This prostration may be contrasted with the maniacal struggles of the patient with meningitis and with leukocytosis, or the thyroid-like activity of the patient with subacute bacterial endocarditis.

3. Concurrent with this loss of strength, perhaps as a part of the same process, and likewise before bacterial invasion, there is a dulling of the mental functions, a falling away of the normal vividness and awareness of the immediate surroundings, a loss of memory, a sleepy silence, then a muttering delirium or a deep unconsciousness. Memory is gone days before death comes.

4. No one has yet accounted for the rising fever of complete granulopenia that comes before sepsis. It is very difficult to state when sepsis begins and one can note its beginning with only relative accuracy. With immunity gone, one does not know how quickly bacteria invade the intestinal wall and pass to the adjacent tissues. The appearance of multiple ulcers in the intestinal mucosa is probably synchronous with the necrosis of the mouth, throat and rectum. Nevertheless, this curious fever precedes the evidence of sepsis. This fact seems to intimate that one of the functions of the granulocytes may be to aid in heat control.

With the loss of immunity to bacteria, the loss of strength, the prostration of the mental functions, the rising fever, and then a quick sepsis, death is inevitable unless a new crop of granulocytes quickly comes back into the blood stream. If in this time of sepsis, the bone marrow reassumes its myelocytic activity, the first evidence in the blood stream is the finding of juveniles and band forms of the granulocytes, myelocytes and in one case myeloblasts. In case 10 myelocytes appeared in the blood two days before any juvenile granulocytes were seen. On the third day of regeneration there were 1350 leukocytes, of which 64 per cent were myelocytes, 8 per cent each of juvenile and band forms, and 20 per cent lymphocytes. Such a preponderance of myelocytes intimates nature's hurry to cure by the only known method—new granulocytes. Without them, sepsis does its perfect work through a blood stream infection, necrosis and gangrene, perhaps hemorrhage, intestinal ulceration, with or without a diarrhea, furunculosis, visceral abscesses, circulatory failure and a terminal bronchopneumonia. Here bronchopneumonia may better be regarded as a combination of localized pulmonary sepsis and circulatory failure.

TREATMENT

Acute incomplete granulopenia is as a rule a far milder condition than the usual fatal acute complete granulopenia. Some authors have not dis-

tinguished between the danger of the two conditions. All 12 of the cases reported in this paper showed an entire absence of granulocytes and were therefore acute complete granulopenias. Ten of the 12 are dead. Only two are living, both women, and one has had two attacks. As long as granulocytes remain in the blood stream, there is probably some myelocytic activity. The resumption of normal activity is a matter of degree of function and the prognosis is more favorable. Good nursing, food, water, fresh air and a watchful, expectant attitude may be all that is wise. The tendency is to do too much and to continue to do too much. Wise clinical judgment at the bedside is better than much long distance telephoning to distant authorities who boost a new and single specific remedy.

It is quite different with a complete granulopenia that comes with the sweep of a clinical storm. The mechanism and series of events in this degree of granulopenia are of ill import for recovery. Complete granulopenia is usually a fatal disease during the first or a later attack. We have not seen either of our two recovered cases return to normal, robust health. An absence of granulocytes in the blood stream means that the bone marrow has ceased its myelocytic activity and that collapse, fever, loss of immunity to bacteria and sepsis are at hand. One is called to treat far more than the apparently simple condition of absent granulocytes. Those who advocate and use specific remedies would do well to realize the enormous power they are claiming for the remedy. What is needed here is judgment of the therapeutic proof by the standards of scientific accuracy.

There are three chief objectives of scientific treatment.

- 1 The maintenance of the life and strength of the patient, much can be done with good nursing, food, air, water and care of the skin, throat, and control of fever.

- 2 The stimulation of the bone marrow to such a degree that it may resume its myeloblastic activity with the production of myelocytes and granulocytes. So far as we know, granulocytes do not function until they slip into the blood stream. There is apparently no known drug or specific remedy that can thus sufficiently stimulate the bone marrow.

- 3 The invitation to an early sepsis as nature's most universally used method to stimulate the myeloblastic activity of the marrow. It is the quickest way known to produce a leukocytosis. Nature uses it with telling effect in nearly all the purulent infections with pyogenic bacteria. The leukocytosis of appendicitis is an example. It is a myeloblastic stimulation that the surgeon calls a leukocytosis. There is no better way to provide it than the way nature provides it. We take the position that even complete granulopenia does not necessarily irreparably damage the marrow to the extent of destroying this important function. The function is in abeyance. After necrosis and sepsis we have seen the granulocytes rise in four days from none to 40,000. In another case with necrosis of the foot, in four days the granulocytes rose to 25,000.

With absent granulocytes and increasing sepsis, it is merely a question whether the patient can survive long enough for the granulocytes to reappear. Sepsis and necrosis are the great hopes of every patient with complete granulopenia. The patient may die from sepsis with maturation proceeding at full tilt in the marrow, but before the granulocytes reach the blood stream. It is well to avoid surgical treatment of the necrotic areas. Such treatment is of no avail until the granulocytes appear in the blood stream, and their reappearance will usually cure the patient and also the sepsis and necrosis.

With no evidence of sepsis and necrosis, one would not do far wrong to inject living staphylococci in the skin, or give 5 to 10 minims doses of turpentine intramuscularly. Kracke has shown that turpentine in this way causes necrosis of muscle tissue and a leukocytosis in the rabbit. One of us (S R R) used this method in one of our surviving cases apparently with a happy effect.

We have used radiation, transfusion, liver extract, pentose nucleotide and foreign protein to no avail. We have seen no result and only disappointment from their use. We have had no experience with adenin sulphate. We see no reason why it should be of aid.

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DRUG IDIOSYNCRASY, WITH SPECIAL REFERENCE TO AMIDOPYRINE, AS A CAUSE OF AGRANULOCYTIC ANGINA *

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THE designation, agranulocytic angina, although etymologically incorrect and scientifically inept, has become firmly entrenched—despite other preferable designations such as “pernicious leukopenia” or “primary granulocytopenia.” It is here employed, in the now generally accepted sense, as designating the syndrome of Schultz. This disorder was at first viewed as a peculiar reaction to some unknown infection, analogous to the previously recognized leukopenia sometimes encountered in overwhelming sepsis. Soon, however, it became clear that the heterogeneous micro-organismal invasion, seen in the majority of cases of agranulocytic angina, is merely a secondary or terminal event and is preceded by profound neutropenia. This led to the current view of agranulocytic angina as a clinico-pathologic entity of undetermined etiology belonging to the group of “blood system diseases”—to be distinguished from, although often simulated by, other types of neutropenia.

The possibility of an allergic mechanism in the etiology of agranulocytic angina has been emphasized in clinical teaching by O. H. P. Pepper since 1928 (after observing several patients afflicted with this disease whose histories indicated clear-cut allergic backgrounds). His first recorded statement of this hypothesis was made April 16, 1930, before the College of Physicians of Philadelphia¹ and was presented in greater detail in a Black Memorial Lecture² at Pasadena in January 1931. In a review of 18 cases of agranulocytic angina published in April 1933 Fitz-Hugh and Comroe³ stated that “additional treatment in all cases included oropharyngeal care, avoidance of drugs that might reasonably produce anaphylactoid reaction (Dr. Pepper’s suggestion), the use of orange juice, vitavose, calcium gluconate, and cod-liver oil.” Following the publication of this article with its specific reference to the possibility of “anaphylactoid” drug dangers, there appeared, quite independently, the epoch-making contribution of Madison and Squier⁴ presenting very strong evidence tending to incriminate amidopyrine medication with resulting allergic or anaphylactoid reaction as a most important cause of agranulocytic angina. Similar reports, altogether constituting a grave indictment of amidopyrine with or without barbituates, have since rapidly accumulated.^{5, 6, 7, 8, 9, 10}

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The recent comprehensive review by Kracke and Parker⁹ of the hypotheses, experimental data, and clinical and laboratory findings relating to etiology makes unnecessary any general recapitulation. Since 1930 Kracke has maintained that drugs containing the benzene ring may be responsible for the disease and especially those belonging to the "benzamine group" amidopyrine, phenacetin, acetanilid, arsphenamine, neoarsphenamine. He has viewed this mechanism as a direct toxic action of some one or more of the oxidation products of benzene (hydroquinone, catechol, orthoquinone and paraquinone) on the bone marrow. His present position, however, includes the hypothesis of a "previously weakened, damaged, or idiosyncratic bone marrow" to account for the obvious facts that only a very few of the many individuals exposed to these substances actually develop the disease, and only an occasional experimental animal exhibits granulocytopenia out of a large group of animals given these drugs or their oxidation products.

In spite of the fact that our clinical staff has been for the past six years aware of the possibility of drug idiosyncrasy in agranulocytic angina and has frequently forbidden this or that drug in any given case where there seemed to be a suggestion in the patient's history of such drug's unfavorable or unusual action (including "allonal" in one early case!), we nevertheless failed completely to recognize the apparently important rôle of amidopyrine until the findings of Madison and Squier came to our attention a few months prior to publication of their paper. The purpose of the present report is to summarize the evidence accumulated in a review of our cases from the standpoint of drug idiosyncrasy, with especial reference to amidopyrine, as a possible cause of agranulocytic angina.

The following statistics and observations are based on a study of 26 cases of agranulocytic angina of which 18 have been previously reported.³ These data were obtained by study of recent patients, by review of hospital and office records, by personal conferences with surviving patients, and by correspondence with patients, relatives, and referring physicians.

The sequence of amidopyrine medication followed by hematologic proof of the diagnosis of agranulocytic angina is present in 14 cases (54 per cent). This same sequence is probably present but unproved in another five cases (19 per cent) and entirely unproved (but not impossible) in another six cases (23 per cent). The sequence is disproved in one case only.

In addition to the 14 proved instances of amidopyrine medication prior to hematologic verification of the disease (seven of whom continued the drug) there are three instances of amidopyrine medication instituted during the course of the disease. Thus 17 patients (65 per cent) are known to have ingested amidopyrine just prior to and/or during the course of the hematologically manifest stage of the disease. Of these 17 patients 13 are dead of the disease (77 per cent mortality) and four are living and well. Of the 13 fatal cases 10 continued and three discontinued ingestion of amidopyrine immediately after the establishment of the diagnosis. Of the

four surviving patients in this group three discontinued at once the ingestion of amidopyrine on establishment of the diagnosis and one discontinued it soon thereafter

Of the five cases listed as "probable but unproved" in relation to prior amidopyrine medication four are dead and three of these received amidopyrine during the course of the disease. Of the six "unproved" cases five died (all "acute cases") without receiving any amidopyrine after hematologic verification of the disease, although the possibility of prior amidopyrine medication can neither be affirmed nor denied with absolute certainty

The one patient in this series in whom amidopyrine medication can be absolutely excluded from all consideration will be discussed in some detail below. The total mortality figures to date are 19 dead (73 per cent), one of unknown status, and six living (three weeks' "cure," six months' "cure," eight months' "cure," three years' "cure," five years' "cure," and one relapsing case at present in good condition)

The preparations containing amidopyrine ingested by these patients are amidopyrine in capsule with other ingredients as prescribed by attending physicians, "pyramidon", "allonal", "peralga", "amytal compound", and "midol tablets"*. In no instance has the dosage of the drug been in excess of the average therapeutic limit. The largest quantity known to have been taken by any one of these patients was 25 grains daily of amidopyrine for seven days immediately prior to hospitalization, when the diagnosis was established. Two patients had used "allonal" and "pyramidon" at irregular intervals and in ordinary therapeutic quantity for several years before the fatal agranulocytic episode which seemed to follow just one more "ordinary dose". One patient had taken a few "midol tablets" for a few days each month for about six months prior to the proved onset of the disease. Another had taken only two "allonal" tablets and four "pyramidon" tablets during the period of 48 hours between a tooth extraction and the proved hematologic onset of agranulocytosis. Another, because of "acute tonsillitis," took a capsule containing two grains of amidopyrine every four hours for three days at the end of which period agranulocytosis was discovered. Our most recent case is that of a pupil-nurse who had taken one to two tablets of pyramidon once a month for about five years for relief of headaches. She had taken none, however, for at least a month until 5-29-34 when she took two tablets and repeated this dose (10 grains) on 5-30-34. Profound neutropenia was discovered on this date. A week later, after hematologic and clinical recovery, this patient was given

* A partial list alphabetically arranged, of proprietary and patented medicaments in which available evidence indicates an amidopyrine content includes "Allonal," "Alphebin," "Amarbital," "Amido-Neonal," "Amidophen," "Amifene," "Am-Phen-Al," "Ampydim," "Amytal Compound," "Baramid," "Barbromide" (Columbus), "Benzedo Compound," "Cibalgine," "Cincopyrine," "Compral," "Dysco," "Gynalgos," "Hexin," "Ipral-amidopyrine," "Kalms," "Lumordrin," "Midol," "Mylin," "Neonal Compound," "Neurodyne," "Optalidon," "Peralga," "Phenamidal," "Pyramidon," "Pyraminal," "Sal-Ethyl Carbonate Compound"

one five-grain tablet of amidopyrine with an ensuing loss of more than one-third of her circulating neutrophils in three hours, followed by prompt recovery

It is obvious that if amidopyrine-idiosyncrasy is a cause of agranulocytic angina we shall have to revise some of our concepts of the disease. In the first place the earliest symptoms of ill health, instead of being true "onset symptoms" of the disease itself in many instances must be viewed as purely accidental disorders which occasion the use of amidopyrine (or other drug) medication. This conclusion is predicated on the fact that several patients had taken no medicine of any kind for many months prior to the onset of distress symptoms which then, and then only, were met with drug (amidopyrine) administration and which seemed to merge promptly and imperceptibly into the ensuing picture of hematologically established agranulocytic angina. Such immediate symptomatic antecedents in these 26 cases are classifiable as follows: pharyngitis, tonsillitis, bronchitis, and "grippal" onset in 13 patients, dental extraction onset in five patients, gall-bladder colic onset in one, abdominal pain onset in one, kidney colic onset in one, postoperative (osteomyelitis) onset in one, neuritis and arthritis onset in two, carcinoma of bladder in one, migraine in three (one of whom is also included in the "grippal onset" group, and another in the abdominal pain group above).

A more fundamental adaptation of generally accepted views is involved in an interpretation of the mechanism of the known blood and bone marrow changes in agranulocytic angina if the drug-idiosyncrasy factor is to be accepted. The evidence in several "acute" cases mentioned above would necessitate the assumption of, first, an almost immediate granulocytoclastic crisis* occurring within a few hours to a few days of the first noxious dose of the drug, and second, a concomitant or subsequent bone marrow disturbance characterized by "maturation arrest" of the myeloid white cells at or below the myelocyte level and in many instances an apparently similar but less complete arrest, at the source, of lymphocyte and monocyte maturation and emigration¹¹. These two assumptions may be made without great violence to our preconceptions. The most difficult piece of evidence, however, to fit into the "drug-idiosyncrasy" hypothesis would seem to be the apparently established fact (Kracke et al.) that granulocytopenia precedes all other clinical phenomena of the disease. This fact would be understandable in the case of habitual users of the drug or drugs in question and would merely necessitate the assumption of suddenly acquired idiosyncrasy, or of previously existing mild and unrecognized episodes of agranulocytosis. It is also understandable in some acute cases if one accepts the hypothesis of certain supposedly early symptoms being merely reasons for medication rather than true onset phenomena of the agranulocytic angina syndrome. But the drug idiosyncrasy hypothesis and the now orthodox

* This term is coined to convey the idea that granulocytes suddenly disappear from the peripheral blood either by rapid elimination, destruction, or retention in internal organs and vessels.

dictum that "granulocytopenia precedes clinical symptoms" would seem to clash hopelessly in the face of certain acute and relapsing cases of the disease which have been reported^{12,13}

In these, and one of our own to be mentioned below in more detail, the neutropenia occurred out of a clear sky without drugs and with no symptoms requiring drug therapy until several days after the "agranulocytic" blood picture was established

That the role of amidopyrine in the etiology of agranulocytic angina is not a simple toxicologic process is obvious, not only from the fact that probably less than one in many thousands of users is afflicted with the disease but also from such considerations as the following (1) none of our patients with agranulocytic angina has taken an excessive quantity, (2) the records of two "allonal" suicides who lived four days and six days respectively, after taking between 30 and 50 tablets of allonal each, show essentially normal blood counts just prior to death, (3) the records of four private patients known for many years as habitual users of allonal (averaging at least two tablets nightly for at least three years) show repeatedly normal blood counts, (4) the records of two patients with measles and three with rheumatic fever each treated with amidopyrine in doses from 20 to 30 grains daily for from four days to three weeks show no granulocytopenia throughout

Other drugs used by our patients, before hematologic diagnosis was established, include aspirin, sodium salicylate, phenacetin, strychnia, phenobarbital, "amytal," sodium bromide, "salicon," "bromo-seltzer" (acetanilid), cinchophen, phenolphthalein, mineral oil, cascara, orthoiodoxybenzoate, quinine, and diphtheria antitoxin. Drugs used after diagnosis was established included many of the group just mentioned and in addition codein sulphate, morphine sulphate, digitals, caffein-sodio-benzoate, and the usual items of treatment of the disease itself (pentose nucleotide, blood transfusions, roentgen-ray, calcium, liver extract, etc., and in two cases neosphenamine)

The one patient in this series concerning whom it is certain that amidopyrine could have had no connection with his repeated bouts of agranulocytic angina is a man whose wife is a physician. This patient had taken a good deal of quinine in some of his attacks of probable agranulocytic angina prior to coming under our care. The important point in this connection, however, is that since then he has had several desperate attacks of "agranulocytosis" each one coming "out of a clear sky" without any medication of any kind (not even mineral oil which our records show to be a most frequent concomitant—though assuredly a blameless one)

This series, like others recently reported, shows a high incidence of patients closely related to practitioners of medicine: one dentist's daughter, one registered nurse, one pupil-nurse, one doctor's mother, one doctor's father-in-law, one dentist, one doctor's husband, two cousins of doctors, one doctor's wife

Six of the 26 patients gave histories indicative of definite allergy three with migraine associated with urticaria or eczema or vasomotor rhinitis, one with asthma, and two with food sensitizations. Two of these allergic individuals and three others (not obviously allergic) gave histories suggestive of drug idiosyncrasy (e.g., "stimulation" from morphine, "weak feelings" from aspirin, "elation and vertigo" from allonal, "depression" from phenobarbital). Skin sensitization surveys made in five cases showed only a few minor food reactions. Blood calcium studies in two patients during and after attacks of agranulocytosis showed no significant abnormalities. "Patch tests" with amidopyrine, acetanilid, acetylsalicylic acid, phenacetin, phenobarbital and morphine sulphate in one recently recovered patient (who had used pyramidon, bromo-seltzer and "empirin compound" for migraine prior to onset of agranulocytic angina) were all absolutely negative (Dr R. A. Kern). "Patch test" with amidopyrine in the most recent case—that of the pupil-nurse—was also negative.

It is clear that there are no valid tests or clinical guides to warn against the possibly noxious drugs in this agranulocytic type of idiosyncrasy, until the disease has already developed. It is then, unfortunately, sometimes too late—as evidenced by the fact that at least three patients, known to have taken amidopyrine prior to onset, and five, in whom there was no such evidence, died of the disease in spite of subsequent rigid proscribing of this and related drugs. The ordinary history of drug idiosyncrasy is untrustworthy at best and is often lacking in these cases. A clinical history of allergy, while possibly significant, is not obtainable in many patients with agranulocytic angina. Better methods of skin testing with drugs may eventually prove helpful but the evidence is not encouraging.

It is thus obvious that some presumptive evidence has been adduced in support of the thesis that amidopyrine idiosyncrasy may be an important cause of agranulocytic angina, but equally obvious that it is not the only cause. Kracke's findings would tend to incriminate any or all of his so-called "benzamine" group.⁹ In addition certain of the "heavy metals" have been suspected (especially gold). One case is now on record following dinitrophenol administered for "reducing" purposes.⁷ One of our cases developed during "oxoate" therapy. Several have been observed after intravenous typhoid vaccine injections and several after quinine administration (including one in this series). On the other hand the barbiturate group, at first suspected along with amidopyrine, has more recently been, at least in part, exonerated.^{14, 15, 16}

An analogous problem is raised in the recent report of thrombocytopenic purpura ascribed to "sedormid" medication in one instance¹⁷ and to "quinine and ergot allergy" in another.¹⁸

Closely related to amidopyrine is phenylhydrazine with its well known hematologic activity. We have never observed severe neutropenia, however, in the course of polycythemia vera under treatment with this drug. Other substances quite similar in chemical structure to amidopyrine and

phenylhydrazine are included in Kracke's "benzamine group" Each of these has from time to time in the past been observed to produce abnormal hematologic conditions other than granulocytopenia¹⁷

Personal records of blood counts obtained during certain ordinary acute drug idiosyncrasy reactions (one morphine-hyperemesis, several varieties of skin rash from iodide, arsphenamine, phenolphthalein, luminal, bromide and phenylhydrazine, two cases of salicylate and quinine tinnitus and one of belladonna sensitivity) show no instance of severe granulocytopenia comparable to true agranulocytic angina The same remarks apply to the leukocyte response in the more usual acute and chronic clinical allergies (bronchial asthma, hay fever, etc) Occasionally, however, severe neutropenia is found in acute serum sickness and in the early phase of protein shock It is also a nearly constant phenomenon of experimental acute anaphylactic shock (dog and guinea pig)

CONCLUSIONS

1 Our evidence suggests that amidopyrine idiosyncrasy may be a contributing "cause" of more than half the cases of agranulocytic angina In this series of 26 patients, 17 are known to have ingested amidopyrine just before and/or during the disease

2 A few well established negative instances, however, prove that amidopyrine cannot be accepted as the sole cause

3 Some of these non-amidopyrine cases may possibly be caused by idiosyncrasy to other drugs and substances (quinine, dinitrophenol, ortho-iodoxybenzoate, neoarsphenamine, bacterial vaccine, etc) or to a similar abnormal reaction ("anaphylactoid") to foods, exogenous or endogenous "toxins" whether chemical or bacterial, or to hormonal substances or a "conditioned deficiency"

4 If the causal mechanism be of idiosyncratic or allergic nature, it must represent a very special blood and bone marrow sequence of events hitherto unrecognized and different from the ordinary clinical and hematologic phenomena usually ascribed to such mechanism From the standpoint of leukocyte behavior the mechanism seems to be more like that of acute anaphylactic shock in laboratory animals than human allergy

5 The therapeutic implications of these findings suggest the advisability of more specific attempts at "elimination" and "detoxification" especially with regard to the liver²⁰ as a possible seat of allergic disturbances

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DIAPHRAGMATIC HERNIA¹

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AN increased interest in diaphragmatic hernia has been stimulated by its growing incidence, by the sharp difference of opinion as to what constitutes one type of herniation at the esophageal hiatus, and by the marked recent increasing measure of success of its surgical treatment.

Diaphragmatic hernia is a protrusion of abdominal viscera through an anatomically weak area or through an abnormal opening or weak area in the diaphragm, the result of imperfect development, anatomical weakness or of trauma. A sac is a component part of a typical hernia, but the great majority of hernias through the diaphragm have no sac. By common usage they are classed as false diaphragmatic hernias.

The diaphragm is a thin, fibromuscular septum between the thoracic and the abdominal cavity. It consists of a peripheral muscular, and a central tendinous portion, and has three large openings, the esophageal, the aortic and the caval. The esophageal is the only one of the three through which hernias occur. It lies at the level of the tenth dorsal vertebra a little to the left of the midline, is oval in shape and is bounded by two muscle bundles from the crurae which rise on either side of the bodies of the upper lumbar vertebrae. The inner halves of these bundles cross one another between the aorta and the esophagus, and then pass to the central tendon. The size of the muscular ring so formed varies somewhat. Hernias occur in the gap bridged by pleura and peritoneum between it and the contained esophagus.

There are two triangular parasternal areas anteriorly, between the attachment of the muscle to the xiphoid and to the cartilages of the seventh ribs where there is a gap in the muscle bridged over by peritoneum (the foramina of Morgagni), through which diaphragmatic hernias occasionally occur.

There are two triangular lumbocostal areas between the attachment of the muscle to the vertebra and the twelfth rib, similarly lacking in muscle and through which a congenital hernia may develop (the foramina of Bochdaleki). After both these areas are protected from pressure by the upper poles of the kidneys and are therefore seldom the sites of an acquired hernia.

Abnormal openings or weak areas may be the result of incomplete or imperfect embryonic development of the structures dividing the single U-shaped celom into pleural, pericardial and peritoneal cavities. This is a complex process beginning in the human embryo 21 mm long. It is brought about through the fusion of several component parts as follows:

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(1) The dorsal mesentery, (2) the septum transversum, situated anterolaterally and ventrally, (3) the pleuro-peritoneal membranes, dorso-laterally, and (4) narrow shelves, peripherally, joining the parts from the pleuro-peritoneal membranes to the chest wall

These structures complete the division of the celom in the embryo of 18 to 20 mm. The muscular component between the pleura and peritoneum is of later, entirely independent origin. The muscle in the central portion at a still later period is replaced by the central tendinous structure. Failure of development of any part of one or more of these formative structures or failure of union of their adjacent parts results in a gap in the partition through which abdominal contents may later protrude into the pleural cavity without carrying before them any membrane or sac.

Absence of the muscular component at any point results in a weak area through which a hernial protrusion into the pleural cavity may develop. If the pleura and peritoneum representing the earlier embryonic structures are present they will form a sac for such a hernia. Similarly a hernia through the esophageal hiatus and at the foramina of Morgagni will have a sac.

Other embryological factors which may contribute to hernia formation are the development of the omental bursa and those factors incident to the relative sizes and changing positions of the stomach, intestines, and liver.

The omental bursae are two finger-like projections of peritoneum into the thick dorsal mesentery on either side of the foregut appearing in the embryo of 3 mm. Normally these projections become constricted off and disappear. If either of them remains open it constitutes a preformed hernia ring and sac.

The stomach originates as an enlargement of the foregut in the thorax in the embryo 11 to 12 mm long. It migrates downward with the elongation of the esophagus and coincident descent of the septum transversum and by the time the diaphragm is complete it normally lies below it. If any portion of it fails to reach its normal position at the time of diaphragmatic closure it will remain intrathoracic. We then speak of the condition as congenitally short esophagus and of a "thoracic stomach." The degree of esophageal shortening and the consequent amount of stomach that remains above the diaphragm vary. The esophagus may be so short that the whole stomach is intrathoracic.

The liver begins as an ingrowth into the septum transversum from the foregut. The anterolateral portion of the diaphragm proper is later split off from the main liver mass of the septum transversum by infolding of the peritoneum, the falciform and coronary ligaments in the adult representing the only portions that remain united. Abnormalities in liver development or in the later normal atrophy of the left lobe may lead to imperfect development of the diaphragm (Broman). Failure of physiological umbilical herniation of the intestines, which normally begins in the embryo 11 to 12 mm long, and which reaches its maximum in an embryo a little more than double that length, failing thereby to relieve increased

intra-abdominal pressure caused by the descent of the septum and rapidly enlarging liver within it, is said by some writers to be a factor in hernia formation

CLASSIFICATION OF DIAPHRAGMATIC HERNIA

Diaphragmatic hernia may be classified on an etiological basis as follows

- (1) Congenital (true or false),
- (2) Acquired (true or false),
- (3) Traumatic (true or false)

A congenital hernia as here understood means one present at birth. The absence of a sac indicates that the hernia opening is due to the failure of development or failure of fusion of one or more of the anlagen of the diaphragm. The presence of a sac composed of pleura and peritoneum is evidence of hernia formation after the complete separation of the pleural and peritoneal cavities.

An acquired hernia signifies one that develops gradually after birth in a congenitally weak area such as at the esophageal opening or at the parasternal or the lumbocostal trigone. It is acquired in the same sense as an inguinal hernia is usually acquired through the anatomically weak inguinal ring. With a few exceptions such hernias have a sac.

A traumatic hernia is one that results from a penetrating injury to the diaphragm, as by a bullet or a shell fragment or a knife stab, or from tearing or bursting of the diaphragm from sudden violent abdominal or thoracic compression, as from a fall, blow or crushing impact, almost all such cases are without a sac. Some writers have excluded recent injuries of the diaphragm with prolapse of abdominal contents, while including those of long standing as diaphragmatic hernia. There seems to be no reasonable grounds for attempting to so distinguish between identical conditions on the basis of duration.

Clinically the differentiation of these etiological types may be difficult. A hernia due to a gap in the diaphragm or one with a sac present at birth is obviously congenital but such a hernia may remain latent for years and then it may be difficult to decide whether it is congenital or acquired. Many writers include the acquired with the congenital. In the study of combined series of cases it is therefore expedient to combine these two groups. A traumatic hernia also may remain latent even if it produces symptoms or signs and may remain unrecognized for years. As a rule, its etiology is evident.

INCIDENCE

If the true incidence is to be deduced from the number of reported cases it is necessary that the diagnosis be certain. Up to recent years there could be no reasonable doubt as to diagnosis. Practically all the earlier reported cases were found at necropsy, a few were confirmed by operation. With the advent of roentgenography the demonstrations of herniation of various

parts of the gastrointestinal tract above the diaphragm also were unmistakable. However, during the last 10 years large series of cases have been reported of "herniation" through the hiatus of a small portion of that part of the stomach just below the terminal esophagus, the diagnosis having been based almost exclusively on a special technic for its roentgenological demonstration. The validity of this technic has been disputed by other observers.

In discussing the incidence of diaphragmatic hernia it therefore seems advisable to segregate the two groups.

The reported incidence of undoubted cases is shown in table 1.

TABLE I

Incidence of Diaphragmatic Hernia Exclusive of Large Series of Esophageal Hiatus Hernias

| Author | Con- genital | Acquired | Trau- matic | Total | Remarks |
|------------------------------|-----------------|----------|----------------|-------|-------------------------------------|
| Lacher | | 127 | 146 | 273 | Exclusive of 6 cases of eventration |
| Thoma (1882) | | 10 | 3 | 13 | |
| Grosser (1900) | | 98 | 48 | 146 | |
| Richards (1924) | 115 | 18 | | 133 | |
| Greenwald and Steiner (1929) | 60 | | | 60 | Exclusive of 22 reported elsewhere |
| Harrington | | 44 | 12 | 56 | 4 reported elsewhere |
| Hedblom (1931) | 116 | 133 | 351 | 600 | Including 26 personal cases |
| Hedblom (1934) | 64 | 36 | 27 | 127 | |
| | | 821 | 587 | 1408 | |

The incidence of "hernias" through the esophageal hiatus is given in table 2.

Åkerlund proposed a classification of esophageal hiatus hernias into three sub-groups: (1) those with a congenitally short esophagus producing the so-called "thoracic stomach," (2) the para-esophageal type in which the lower end of the esophagus remains fixed and variable amounts of stomach herniate through the ring along side of it, (3) those in which the lower end of the esophagus with more or less of the stomach prolapses through the opening—the "hiatus hernia" of Åkerlund.

"Thoracic stomach" is relatively rare. Only about 20 are reported. The para-esophageal, though generally accepted as a clinical and pathological entity, also seems to be relatively uncommon. The great majority of the cases reported belong to the third type. It has rarely been recognized at necropsy and has been overlooked on roentgenological examinations with

TABLE II

Incidence of Esophageal Hiatus "Hernias" Diagnosed Chiefly Roentgenologically and Largely Unconfirmed by Operation or Necropsy

| Author | Year Reported | Number of Cases |
|--------------------------|---------------|-----------------|
| Camman and Fineman | 1924 | 17 |
| Healy and Morrison | 1925 | 53 |
| Jenkinson | 1925 | 25 |
| Åkerlund, Ohnell and Key | 1926 | 25 |
| Pancoast | 1926 | 11 |
| Ude and Rigler | 1929 | 19 |
| Ritvo | 1930 | 60 |
| Berg | 1930 | 60 |
| Knothe | 1932 | 300 |
| Schatzki | 1932 | 23 |
| Velde | 1932 | 16 |
| Koeppen and Frank | 1932 | 20 |
| | | 629 |

the patient in the routine upright position. According to Åkerlund and others, who have reported large series of them, this is due to the usual spontaneous reduction of the herniated sac or its contrast media content, especially by gravity in the upright position. According to these writers its roentgenological demonstration requires that the patient be examined in the horizontal or partly inverted position and in some cases it also requires increased intra-abdominal pressure as produced by straining, by manual pressure, by constricting the abdomen, or by inflating the colon.

By such methods, Knothe, in von Beigmann's clinic, was able to demonstrate a "hiatus hernia" in 300 patients during one year, representing 8 per cent of all patients subjected to special gastrointestinal examination or such as were suspected of having a hernia. Koeppen and Frank found the condition in 20 (16.6 per cent) of 120 people, Velde in 16 (2.3 per cent), Schatzki, by inflating the colon to increase intra-abdominal pressure demonstrated the typical roentgen-ray in 23 (73.3 per cent) of 30 old people examined. It is thus evident that the proportion among different observers varies greatly.

The most direct evidence of the presence of a relaxed muscular and fibrous ring predisposing to herniation is offered by a series of observations, reported by Harrington, on 500 patients in whom the hiatus was palpated during the course of abdominal examination. He found the muscular ring snug about the esophagus in 65 per cent. In 35 per cent at least one finger could be insinuated between the muscular ring and the esophagus. In 5 per cent of this group three fingers could be inserted. All of this last group were subjected to special roentgenological examination for a hiatus hernia and "occasionally a small hernia was demonstrated."

The unprecedented number of cases reported by a few observers, many found in apparently normal individuals, the rarity of the condition in routine postmortem examinations, and the absence of confirmation of the roent-

genological diagnosis at operation or postmortem, except in a very few instances,* has naturally raised the question as to the validity of the roentgenological criteria on which the diagnosis of the hiatus hernia is based. According to Knothe these are (1) the recognition of the typical striations produced by gastric mucosa above the level of the diaphragm, (2) the constriction marking the border line between the stomach and esophagus lying above the diaphragm, (3) the shortening of the sub-diaphragmatic portion of the stomach, (4) the upper part of the stomach is displaced, the fornix disappearing, (5) the esophagus appears relaxed.

Some have interpreted the shadows in question as a normal dilation of the lower esophagus, denying that the folds are sufficiently distinctive to warrant the assumption that they are gastric. Others hold that there may be a shortening of the esophagus during swallowing with a consequent luxation of the part of the stomach just below the hiatus, but that the diaphragm in the immediate vicinity is also lifted into the form of a cone so that while a part of the stomach is lifted above the general level of the diaphragm, it still lies below the cone shaped part. As a result of further roentgenological, clinical, anatomical and pathological studies by Berg, Heinenheiser, Koppstein, Schatzki, Bergmann, Sauerbruch and his co-workers, Stadtsmüller and Creberg, Anders and Bahrmann and others a difference of opinion is evident as to the limits of the anatomical variation about the hiatus and as to the part that the physiological swallowing reflex plays in the production of the changes in shape and position of contrast media in the lower esophagus as observed under the fluoroscope. There is also a difference of opinion as to the significance of the changes produced by inspiration and expiration on the bolus of contrast media at the hiatus and as to whether or not the large striations seen in the roentgen-ray and characteristic of gastric wall are always a reliable criterion. Whether or not, under the various conditions of observation, there does exist an actual herniation of a small portion of the stomach through the hiatus, it seems pretty certain that such a hernia if present assumes practical importance only when it produces definite symptoms. In a great majority of cases any symptoms that may be present are mild and not with certainty referable to the condition.

LOCATION OF THE HERNIA OPENING

The location of the hernia opening was specifically mentioned in 728 of the collected cases of Lacher, Grosser, Richards, Greenewald and Steiner, and the author. In more than 78 per cent of the non-traumatic cases it was on the left side. Of this group more than one-quarter were at the esophageal hiatus, about the same proportion posteriorly and about one-sixth were central. Of the 22 per cent on the right side, about one-quarter were centrally situated, about one-quarter were posterior and nearly one-third at the parasternal foramen.

* Åkerlund reports eight of his original series confirmed later by necropsy.

Of the traumatic hernias, about 95 per cent were on the left side, nearly one-half were lateral and nearly one-quarter central, half of those on the right side were central

Half of the bilateral hernias were at the parasternal opening. So-called bilateral esophageal hernias usually involve a bilateral distribution of the sac through a common opening

Hernias at the parasternal opening are of special importance from the standpoint of surgical treatment. Those with a sac through the foramen of Bochdaleki are uncommon. A sac was present in only four of 60 children and in six of 19 adults in whose cases its presence or absence was mentioned. Those posteriorly situated without a sac are due to failure of closure of the pleuroperitoneal membranes and so are present before the development of the foramen of Bochdaleki. They are therefore not through this foramen

About one-quarter of the non-traumatic hernias situated centrally had a sac indicating a faulty development either of muscle or of later tendon formation in this region rather than a failure of closure or union of the anlagen of the diaphragm. The instances of subtotal or total absence of the diaphragm were mostly necropsy findings in infants. A small proportion survive to adult age

The hernia contents may be a single abdominal viscus or may include any or all the abdominal organs except those in the pelvis. In a series of 857 cases there were 72 different combinations of herniation of the stomach, intestines, colon, omentum, spleen, liver, pancreas and kidney. The stomach alone was herniated in 160 cases (20.0 per cent), the colon alone in 86 (10.3 per cent), the omentum alone in 65 (9.5 per cent), the liver alone in 14 and the spleen alone in two

A typical esophageal hiatus hernia contains usually the cardiac portion of the stomach, one at the parasternal foramen, a loop of transverse colon. In a right-sided hernia except those at the esophageal hiatus and parasternal foramen the hernia content is usually some portion of the liver

ETIOLOGY

There seems to be no sex predisposition to congenital hernia. In a series of 124 infants the sex distribution was equal. There is a preponderance of females with acquired hernia at the esophageal hiatus, nine-tenths of traumatic hernias are in males

There is a marked difference in age incidence of the different types. Of the congenital hernias included in a series of 743 cases about one-third died before reaching one month of age. The great majority of patients with acquired hernias are past middle age, when the hernia is recognized. More than two-thirds of the patients with traumatic hernia are in the second, third and fourth decades of life

Among the congenital cases there is a frequent association of other anomalies of development such as harelip, cleft palate, patent ductus ar-

teiosus of foramen ovale, abnormal or imperfect development of lung, liver or of mesenteric relationships, abnormal cranial development and monstrosities of various types

The direct cause of congenital hernia openings is faulty development of the diaphragm, the specific cause of which is uncertain. It seems reasonable to believe that any one or more of a number of factors involved in the growth and shifting relationships of the anlagen of the diaphragm and of the adjacent organs may contribute to its imperfect or incomplete formation, but the frequent coexistent anomalous development elsewhere suggests the presence of a more general cause.

The most manifest direct cause of hernia formation through the esophageal hiatus, the parasternal foramen and through other areas deficient in muscular support is probably increased intra-abdominal pressure, such as that due to straining at stool, or during micturition, coughing, vomiting, labor, or due to a sudden muscular straining or sudden wrench. Mechanical factors that increase intra-abdominal pressure such as pregnancy, kyphosis, megacolon, have been repeatedly observed in relation to hernias of this type.

Weakening of the diaphragm muscle and absorption of fatty deposit between the serous membranes (in esophageal hernia) are believed to contribute to hernia formation especially in women.

Traumatic lesions may be due to penetrating injuries or blunt trauma. In a series of 318 civilian traumatic cases 165 (52 per cent) were due to penetrating injuries and 153 (48 per cent) to blunt trauma. Of the penetrating injuries 116 (20.3 per cent) were stab wounds, 35 (21.3 per cent) gunshot wounds and eight followed operation for empyema, at least some of which were probably due to operative injury to the diaphragm. Two cases were associated with fractured ribs. Of the non-penetrating injuries 66 (36.6 per cent) were due to falls, 35 (22.8 per cent) to crushing impact, 15 (10 per cent) injuries of the "jack knifing" type by falling weights. In 16 instances some type of violent strain was given as the cause.

In a series of 127 hernias due to war injuries, 44 were due to bullets, 32 to shell fragments and two to bayonets. In 49 the cause was not stated.

SYMPTOMS

There is no entirely characteristic symptom or syndrome. There is a great variation in the symptoms produced by the same type, as well as by different types of hernia. Age incidence, pathogenesis and pathological anatomy determine certain group characteristics, but a hernia of any type may remain symptomless, being discovered at operation for other conditions or at necropsy. The first symptoms in a hernia of years' duration may be those of an acute obstruction.

Symptoms caused by the hernia are often misinterpreted, and the patient treated on the basis of a false diagnosis. The importance of familiarity with the varied clinical manifestations lies not so much in that it will lead

to a diagnosis independently as in that it will suggest the necessary further study to establish the diagnosis

The symptoms naturally group themselves into those referable to the thorax and to the abdomen, respectively. The size and position of the hernia contents determine in large measure the thoracic symptoms, and the hernia content and differing degree of hernia ring constriction account largely for the wide range of abdominal symptoms

Dyspnea, cyanosis, palpitation and a feeling of fullness or of suffocation, dysphagia, pain under the sternum and in the shoulder, and coughing are the most common thoracic symptoms. Hiccough is occasionally present. Dyspnea, palpitation and a feeling of fullness occur most characteristically after heavy meals or after drinking a large amount of fluid. Many patients are unable to lie down immediately after meals on account of such symptoms. Some induce vomiting or pass a stomach tube on themselves for relief of this distress. Some patients speak of a subjective feeling of the presence of fluid, of gurgling or of splashing in the thorax, others of a sense of impending disaster in connection with a feeling of suffocation. Some patients have more difficulty swallowing liquid than solid food.

The most characteristic abdominal symptoms are those of indigestion of a character more or less suggestive of peptic ulcer or of gall-bladder disease. Nausea and vomiting are common, hemoptysis and melena occasional.

Certain types of hernia have fairly characteristic symptoms. An acquired hernia at the esophageal hiatus usually produces only mild symptoms of indigestion, or more or less dysphagia, but there may be a variety of symptoms of severe grade, including such as are very suggestive of angina pectoris.

Hernias of the parasternal opening containing most often a loop of colon are characterized by constipation and colicky pains. If the loop of herniated bowel is large there may be dyspnea, a sense of suffocation and palpitation.

The immediate symptoms of a traumatic hernia may be due to the injury as such—shock, hemorrhage, pneumothorax. The later symptoms are determined largely by the size, shape and position of the hernia opening and by its content.

Symptoms of obstruction when present are similar to those due to other causes, but an associated dextrocardia and retracted abdomen are almost diagnostic of diaphragmatic hernia as cause of the obstruction.

PHYSICAL FINDINGS

The physical changes produced by diaphragmatic hernia are chiefly thoracic and due to the pressure of the abdominal viscera in the thorax. A bulging of the thorax and decreased respiratory excursion on the affected side, changes in the percussion note and in the auscultatory findings suggestive of pneumothorax, or of a pleurisy with or without effusion, or of

pulmonary cavitation are the most common. A variation of the physical findings, particularly those of auscultation and percussion following change in position and following the taking of fluid or food, is very suggestive of hernia. Borborygmi over the thorax is pathognomonic if eventration can be excluded. Cardiac displacement is very common. A scaphoid abdomen is occasionally observed.

DIAGNOSIS

Before the advent of roentgenography the intravital diagnosis of diaphragmatic hernia was rare. Bowditch in 1854 made the first diagnosis in the living. Lichtenstein in 1874 wrote that of 345 cases he had collected up to that time, only two cases had been recognized clinically, and he reported the first case diagnosed on purely objective grounds. In 1912 Giffin collected 650 cases, among which the diagnosis was made during life in only fifteen.

With the more general use and greater efficiency of roentgenological examination, an increasing proportion are diagnosed clinically but often only after the hernia has been present for many years. Of 82 cases in children collected by Greenewald and Steiner, intravital diagnosis was made in 27, but in only six clinically, 21 were diagnosed by routine roentgenological studies, 47 were found at necropsy, four were diagnosed at operation.

Traumatic hernias are often overlooked. Of 127 soldiers wounded in the late war who were later found to have traumatic hernia, over 40 per cent had symptoms for one to 15 years before the diagnosis was made. A large number of cases are recorded of acute obstruction, years after penetrating injury or blunt trauma, found at operation or necropsy to be due to diaphragmatic hernia.

Symptoms and signs as described, referable to the thorax and abdomen, not accounted for on other grounds, especially with a history of trauma of severe grade or in the presence of scars of a penetrating injury of the lower thorax, should always suggest the possibility of diaphragmatic hernia.

ROENTGENOLOGICAL DIAGNOSIS

Positive diagnosis usually rests on the roentgenological findings. The ordinary fluoroscopic or roentgenographic examination may furnish very strong evidence in the form of localized areas of rarefaction or of consolidation suggesting localized pneumothorax, pleuritis, eventration, hydro-pneumothorax or of multiple cavities in the lung. Positive proof usually rests on the demonstration of a portion of stomach or bowel above the diaphragm following a barium meal or enema. The conditions which simulate hernia most closely on such roentgenological examination are esophageal diverticulitis and eventration of the diaphragm.

Esophageal diverticulitis is usually distinguishable by fluoroscopic demonstration of the filling of the diverticulum first, whereas in hernia of the

stomach through the esophageal hiatus the opaque medium passes through the cardia into the abdominal portion of the stomach and then into the herniated portion

Eventration may be very hard to differentiate. It requires the demonstration of the crescentic shadow of the eventrated diaphragm above the abdominal viscera, the immobility or paradoxical respiratory movement of the affected half of the diaphragm and the identification of the gas or contrast media filled stomach under it.

Failure of demonstration of the stomach or bowel above the diaphragm does not exclude the possibility of hernia. The hernia protrusion may be spontaneously reduced at the time of the examination, or the contrast medium may fail to enter the herniated portion, or a solid viscus only (omentum, liver, spleen) may be herniated.

As stated above a herniated portion of the stomach or a small real esophageal hiatus hernia is usually spontaneously reduced when the patient assumes the upright position, and such hernias therefore are usually overlooked in routine roentgenological examinations. Spontaneous reduction may occur also in other types. Examination for diaphragmatic hernia should therefore be made in the horizontal or Trendelenburg position.

The differential diagnosis of diaphragmatic hernia involves consideration of the commoner abdominal disease conditions such as peptic ulcer with its sequelae, carcinoma of the esophagus and of the stomach, gall-bladder disease and partial or complete obstruction from any cause, and also those conditions of the thorax giving somewhat similar physical findings, such as pleuritis with or without effusion, pneumothorax, pulmonary cavitation, and angina pectoris.

COMPLICATIONS

The most common complications are acute intestinal obstruction and its sequelae, and acute respiratory failure. Gastric ulcer is common. Shock and hemorrhage are especially associated with the trauma causing rupture.

The transverse colon is the portion of the bowel most often strangulated from constriction in a small hernial ring. Either large or small intestine, however, may become gangrenous and perforate due to obstruction of blood supply as a result of volvulus or torsion.

Acute respiratory failure as mentioned is most common in infants with congenital hernia, but may occur in adults with hernia of any type. Many cases of sudden death from asphyxiation are recorded (Fishback, Granzow). The herniated stomach or bowel may be enormously dilated.

TREATMENT

The treatment of diaphragmatic hernia is surgical repair. Relative unfamiliarity with the condition, uncertainty of diagnosis, the frequent technical difficulties incident to its surgical repair and the relatively high

postoperative mortality in the past have combined to create in the medical profession an attitude of false conservatism with respect to surgical treatment. Postoperative deaths from obstruction have been unjustly attributed to the operative procedure.

The mortality in obstructed cases is about two and one-half times that of those operated upon before this complication has developed. A great many instances are recorded in the literature of persistent expectant treatment in the face of recurrent attacks of symptoms characteristic of impending obstruction, which finally developed, the patient dying from it, not infrequently after an operation performed in extremis.

Many patients are allowed to drag on indefinitely as semi-invalids, some incapacitated by nervous instability, some reduced to living skeletons from inability to swallow food or from persistent vomiting.

INDICATIONS FOR OPERATION

The indications for operation should be considered in terms of the severity and gravity of the symptoms as such and in terms of the relative danger of complications and of operation in any given case.

The possibility of saving many of the infants with congenital hernia is suggested by reported successful cases. Since 1931 there are reported nine cases of infants under one year of age operated upon for the repair of the hernia. Six (66.6 per cent) recovered, in one case the opening was too large for closure, two died, one of nine months, and one "new born." One cured case operated upon by Carylles was 13 days old, one successfully operated upon by Johnson and Bower was forty-one and a half hours old. This, it is believed, is the youngest case on record. Five cases between five and 10 years of age and one 13 years of age were cured.

Most congenital hernias in older individuals are posterior or posterolateral. The opening may be assumed to be small if only a part of one viscus is herniated. If a large portion of the abdominal viscera are herniated it still may be small, but it is likely to be relatively large. If the opening is too large for primary closure it may be closed by a muscle or fascia plastic procedure, or by preliminary thoracoplasty combined with some plastic repair.

An acquired hernia ring at the esophageal hiatus may be relatively inaccessible and the edges of the ring may be ill defined, making the closure difficult. If the hernia is small and producing no marked symptoms, operation is hardly indicated, but if relatively large or producing rather marked symptoms it should be repaired.

Acquired hernia at the parasternal opening usually produces relatively severe symptoms due to partial obstruction of the colon and to crowding of the heart and lungs. The hernia opening is quite accessible through an epigastric incision. Such a hernia should be repaired unless there are very definite contraindications to operation.

Penetrating injuries in the chest wall from the sixth interspace down should be explored for injury to the diaphragm and abdominal viscera if there is any probability of deep penetration. If symptoms persist following severe blunt trauma, and roentgenological examination shows hernia, immediate repair is advisable.

Preliminary operations include enterostomy, phrenic nerve crushing and thoracoplasty. An enterostomy may be life saving in acute obstruction, the hernia being repaired at a later date. Phrenic nerve crushing will facilitate the closure of a large hernia opening centrally or peripherally situated. In case of an esophageal hiatus hernia it is of less value and in case of a parasternal hernia it is not necessary and may be harmful in that it is impossible to determine clinically through which parasternal opening a right or left sided hernia sac protrudes.

Preliminary thoracoplasty is indicated if clinical study or exploratory operation has disclosed an opening too large for direct or plastic closure.

Among 57 cases reported during the last three years the immediate result was good in 72 per cent. There were eight deaths (14 per cent). In the author's series of 22 cases operated upon there were two operative deaths, one from infection, and one, a puny child of four and one-half years, from shock.

SUMMARY

1 Diaphragmatic hernia may be present at birth, it may be acquired through anatomically weak areas, or it may result from direct injury to the diaphragm, or from sudden accidental greatly increased intra-abdominal pressure.

2 There is an increasing incidence of reported cases, particularly of those of the acquired type at the esophageal hiatus and of those incident to wounds and automobile accidents. The greatest increase in incidence is that of the small so-called reducible hiatus hernias demonstrable only by special technic of roentgenological examination, and the inclusion of which as diaphragmatic hernia is challenged by many observers.

3 The exact etiology of the congenital type is not known, that of the acquired type is chiefly increased intra-abdominal pressure in the presence of a congenitally weak area of the diaphragm or an acquired weakness due to atrophy of muscle and absorption of fat deposit in the anatomical foramina.

4 The symptoms are referable to the thorax or abdomen or both in varying proportions and degree. The thoracic symptoms are due largely to interference with the functions of respiration or circulation or both. Abdominal symptoms are largely attributable to a greater or lesser degree of obstruction of stomach or bowel.

5 The physical findings are chiefly thoracic and due to the presence of the herniated viscera. Borborygmi, partial dextrocardia and variable physical findings, especially with changes in position, are particularly significant.

6 The diagnosis is confirmed by the demonstration of an abdominal viscus above the diaphragm. A gas filled viscus may be recognizable, one containing a contrast medium, except in case of a hiatus hernia, is unmistakable. Failure to demonstrate a hernia does not exclude it.

7 Small, reducible, symptomless hernias at the esophageal hiatus should be treated expectantly. The treatment of all other types is surgical repair unless contraindications are present outweighing the indications for operation in the individual case.

8 Intestinal obstruction is the most serious complication and operation in its presence more than doubles the operative mortality.

9 Among 57 cases operated upon, reported during the last three years, there were eight deaths, a mortality of 14 per cent.

10 In the author's series of 22 cases operated upon there were two operative deaths, one from infection, and one, a puny child of four and a half years, from shock.

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THE "Q" DEFLECTION IN NORMAL AND ABNORMAL HUMAN ELECTROCARDIOGRAMS*

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SINCE Pardee,¹ in 1930, re-directed attention to the Q-wave and reported a relative frequency of large Q's, in cases that showed coronary artery disease, there has been an increased effort directed toward the determination of the significance of Q and, more particularly, of a large Q₃. All such work in the Q-wave has been based on the assumption that the term Q, or Q₃, designates a more or less definite part of the electrocardiogram, and that it probably refers to the activation of a fairly definite part of the heart. In this paper we shall attempt an analysis of the Q-wave in normal records and in records of the large Q₁ type that will indicate the relative time occupied by Q. We feel that this time data throws light on the significance of the large Q-wave.

METHOD

For the identification of the parts of the ventriculogram in the three standard leads that correspond in time we have made use of Einthoven's formula as follows: when on any and every vertical line the electrocardiographic curve can be superimposed so that the height in Lead I added to that in Lead III gives the height in Lead II, the time relations are identical.

In all electrocardiograms studied we measured the size of positive deflections from the top of the base line and that of negative deflections from the bottom of the base line. When the figure for Q₁ algebraically added to that for Q₃, gave, with reasonable accuracy, the height of Q₂, it was assumed that Q₁, Q₂ and Q₃ occupied the same time interval. When the size of Q₂ differed grossly from the algebraic total of Q₁ and Q₃, it was assumed that Q₁, Q₂ and Q₃ did *not* occupy the same time interval. Similar calculations were used for R and S. When Einthoven's equation did not balance for one wave, e g , Q₁ plus Q₃ greater than Q₂, while the algebraic total of *all* deflections in Lead I added to the algebraic total in Lead III gave the total in Lead II ($(Q_1 - Q_3) - (R_1 - R_3) - (S_1 - S_3) = (Q_2 - R_2 - S_2)$), it was concluded that summation had taken place so that one wave corresponded to either more or less of the time part occupied by the wave of the same name in another lead—Q₃ for example, corresponding in time to Q₁ plus part of R₁.

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The method outlined above enables one to identify peaks that coincide in time in the three standard leads of an electrocardiogram, and, when they do not coincide, to find the points in the other two leads that do correspond in time with a given peak. In figure 2A, for example, the peak of Q_3 corresponds in time with R_1 and we, therefore, conclude that Q_3 and R_1 represent the same moment and the same process in the heart.

NORMAL ELECTROCARDIOGRAMS

We analyzed electrocardiographic tracings taken from 28 student nurses at the Jewish Hospital in whom there was no clinical evidence and no history to suggest the possibility of heart disease. Three of these records showed a deviation of the main axis to the left, including one large Q_3 and one small Q_3 . Twenty-five of these records showed a normal axis deviation. The Q, R and S waves appeared to occupy the same time interval in 14 of the group of 25 (56 per cent) (Table 1). In the other nine cases Q_1 plus Q_3

TABLE I
Normal Records in Which $Q_1 + Q_3 = Q_2$, $R_1 + R_3 = R_2$, $S_1 + S_3 = S_2$

| Record Number | "Q" | | | "R" | | | "S" | | |
|---------------|------|----------|------|------|----------|------|------|----------|------|
| | I | Leads II | III | I | Leads II | III | I | Leads II | III |
| 2 | 0 | -0.5 | -0.5 | +6.5 | +8 | +2 | 0 | -0.5 | -0.5 |
| 4 | 0 | -0.5 | -0.5 | +6 | +12 | +6 | 0 | -0 | -0 |
| 6 | 0 | -0 | -0 | +2 | +5 | +3 | 0 | -1 | -1 |
| 10 | -1 | -1 | -2 | +7 | +8 | +1 | -0.5 | -0.5 | -0 |
| 12 | -0.5 | -0.5 | -0 | +3.5 | +9.5 | +6 | -1.0 | -0.5 | -0 |
| 13 | 0 | -0.5 | -0.5 | +1.5 | +12.5 | +11 | -1 | -1 | -0 |
| 14 | 0.5 | -0 | -0.5 | +7.5 | +9 | +2 | 0 | -0 | -0.5 |
| 15 | 0 | -1 | -1 | +3.5 | +9.5 | +6 | -0.5 | -0 | -0 |
| 17 | 0 | -0.5 | -0.5 | +3.5 | +7 | +3.5 | -1.5 | -1.5 | -0 |
| 18 | 0 | -0 | -0 | +3.5 | +5 | +2 | 0 | -1.3 | -1.3 |
| 20 | 0 | -0 | -0 | +3 | +4.5 | +1 | -1.5 | -2 | -0.5 |
| 21 | -0.5 | -0.5 | -0 | +4.5 | +7 | +2.5 | -0.5 | -0 | -0 |
| 23 | 0 | -0.5 | -0.5 | +3 | +5 | +2 | -1.5 | -2 | -1.5 |
| 24 | -0.2 | -0.2 | -0 | +2.5 | +8 | +5.5 | 0 | -0 | -0 |

equalled Q_2 in six (table 2). In all, therefore, Q_1 , Q_2 and Q_3 appeared to occupy the same time interval in 20 of 25 tracings (80 per cent). There were four records with no Q-wave. If these are omitted, Q_1 , Q_2 and Q_3 appeared to agree in time in 16 of 20 tracings (80 per cent). The five cases in which Q_1 plus Q_3 did not equal Q_2 are presented in table 3. In these there appeared to be summation so that Q in one lead corresponds to Q plus part of R in another lead. Q, however, is small in all of these five curves and occupied, at most, insignificant parts of the time taken in other leads by the first part of R. *These results suggest that for practical purposes the term Q represents a definite time interval in normal electrocardiograms.* Examination of the S-wave in this series of normals revealed

TABLE II
Normal Records in Which $Q_1 + Q_3 = Q_2$ but $S_1 + S_3$ does not = S_2

| Record Number | "Q" | | | "R" | | | "S" | | |
|---------------|------|----------|------|-----|----------|-----|------|----------|------|
| | I | Leads II | III | I | Leads II | III | I | Leads II | III |
| 3 | -0.5 | -0.5 | -0 | +6 | +7.5 | +3 | -1.5 | -0.5 | -0 |
| 11 | 0 | -1 | -1.2 | +5 | +10 | +8 | -1.2 | -0 | -0 |
| 16 | 0 | -0.5 | -0.5 | +4 | +9 | +7 | -1.5 | -0 | -0 |
| 22 | 0 | -0 | -0 | +4 | +7 | +6 | -4 | -1.0 | -0 |
| 9 | -0.5 | -1 | -0.5 | +6 | +12 | +5 | -1 | -0 | -0 |
| 5 | 0 | -0 | -1 | +6 | +10 | +5 | -2 | -2 | -0.5 |

TABLE III
Normal Records in Which $Q_1 + Q_3$ does not = Q_2

| Record Number | "Q" | | | "R" | | | "S" | | |
|---------------|------|----------|------|------|----------|------|------|----------|-----|
| | I | Leads II | III | I | Leads II | III | I | Leads II | III |
| 1 | 0 | -1 | -2 | +6 | +13 | +8 | 0 | -0 | -0 |
| 19 | -0 | -0.5 | -1.5 | +3 | +11 | +8.5 | -0.5 | -0 | -0 |
| 25 | -2 | -1 | +0 | +8 | +9 | +3 | 0 | -0 | -3 |
| 7 | -0.5 | -0 | -0 | +3.5 | +7 | +3 | -0.5 | -0 | -0 |
| 8 | 0 | -0.5 | -1 | +2.5 | +8 | +8 | -2 | -0.5 | -0 |

gross lack of correspondence between S_1 , S_2 and S_3 in eight of 25 tracings (32 per cent). In some of these tracings S was large (up to 57 per cent of the height of the largest deflection) and could include significantly large parts of the curve that would correspond in time to R in other leads. These results indicate that S cannot be regarded as representative of a definite time division in normal electrocardiograms.

ELECTROCARDIOGRAMS WITH A LARGE Q_3

In an examination of 1200 consecutive electrocardiograms taken at the Jewish Hospital, 50 (4 per cent) were found which show a large Q_3 according to Pardee's criteria, i.e., Q_3 represents 25 per cent or more of the maximum deflection of Q - R - S , and there are no S_3 's. Waves of the M and W types are omitted. The size of each deflection in this series is given in tables 4 and 5.

Analysis of these records in the manner in which the normal records were analyzed shows that there is no algebraic relation between the total of Q_1 and Q_3 and the height of Q_2 , or between the total of R_1 and R_3 and the height of R_2 , or between the total of S_1 and S_3 and the height of S_2 . A relationship does appear, however, when the algebraic total of all waves in Lead I is added to that for all waves in Lead III. The grand total obtained approximates more or less closely the algebraic sum of the deflections in Lead II.

TABLE IV
Large Q_3 Series Showing Q_3 's That Include Main Phase and Initial Phase

| Record Number | "Q" | | | "R" | | | "S" | | |
|---------------|------|----------|------|-------|----------|-------|------|----------|-----|
| | I | Leads II | III | I | Leads II | III | I | Leads II | III |
| 7748 | -0 5 | -1 | -2 5 | + 8 | + 9 | + 3 5 | 0 | -0 | -0 |
| 7696 | 0 | -2 | -5 5 | +10 | +15 | + 6 | -1 5 | -0 | -0 |
| 7655 | 0 | -2 | -5 | +12 | +13 | + 5 | -1 5 | -0 | -0 |
| 7595 | -0 5 | -0 5 | -2 | + 6 5 | + 6 | + 2 | 0 | -0 | -0 |
| 7521 | -0 5 | -0 2 | -4 | + 7 | + 5 | + 3 | -0 5 | -0 | -0 |
| 7534 | 0 | -1 | -4 2 | + 4 | + 3 | + 4 | 0 | -0 | -0 |
| 7553 | 0 | -2 2 | -5 | + 4 | + 2 5 | + 4 5 | -1 5 | -0 | -0 |
| 7567 | -0 2 | -0 2 | -3 4 | + 6 5 | + 6 | + 5 | -3 | -2 | -0 |
| 7584 | 0 | -1 5 | -3 | + 3 5 | + 2 | + 3 5 | -1 | -0 | -0 |
| 7585 | 0 | -2 | -5 | +12 | +14 | + 6 | 0 | -0 | -0 |
| 7489 | 0 | -2 | -7 5 | +15 | +13 | + 4 | 0 | -0 | -0 |
| 7500 | 0 | -2 | -7 | +15 | +12 | + 4 5 | -1 5 | -0 | -0 |
| 7278 | 0 | -1 | -4 | + 7 | +16 5 | +16 | -0 3 | -0 | -0 |
| 7313 | 0 | -2 | -5 | + 5 | + 3 | + 2 5 | 0 | -0 | -0 |
| 7340 | -0 3 | -1 | -3 2 | + 6 | +12 | + 7 5 | -2 | -0 | -0 |
| 7255 | 0 | -1 | -3 | +12 | + 7 5 | + 4 | -4 | -1 | -0 |
| 7126 | 0 | -0 3 | -3 | + 7 | + 5 5 | + 2 | 0 | -0 | -0 |
| 7067 | 0 | -0 | -1 5 | + 2 5 | + 2 | + 4 6 | -4 | -0 | -0 |
| 6962 | -1 | -0 5 | -3 | + 6 | + 6 2 | + 5 5 | -3 | -0 5 | -0 |
| 6967 | 0 | -1 | -3 | + 1 6 | + 4 2 | + 3 5 | -4 | -0 | -0 |
| 6858 | 0 | -1 | -2 5 | + 7 | + 7 5 | + 2 | 0 | -0 | -0 |
| 6859 | 0 | -3 | -9 2 | +10 | + 6 | + 3 4 | 0 | -0 | -0 |
| 6906 | 0 | -1 2 | -3 | + 4 | + 3 | + 2 5 | -0 5 | -0 | -0 |
| 6716 | 0 | -1 5 | -2 5 | + 6 | + 6 5 | + 4 | -1 | -0 | -0 |
| 6813 | 0 | -0 2 | -5 | +11 | + 8 | + 2 5 | 0 | -0 | -0 |
| 6747 | -0 2 | -0 2 | -2 | + 4 | + 3 4 | + 3 | -1 | -0 | -0 |
| 6751 | 0 | -0 2 | -2 | + 6 | + 6 | + 3 | 0 | -0 | -0 |
| 6557 | 0 | -0 2 | -5 5 | +14 | +17 | + 9 5 | -4 | -0 2 | -0 |
| 6575 | 0 | -2 | -9 | +12 | +15 | + 9 5 | 0 | -0 | -0 |
| 6588 | -2 2 | -5 4 | -4 5 | + 9 | +12 | + 6 | 0 | -0 | -0 |

TABLE V
Large Q_3 Series Showing Q_3 's That Consist Almost Entirely of the Main Phase In many $Q_3 = R_1$ and $R_3 = S_1$ in time

| Record Number | "Q" | | | "R" | | | "S" | | |
|---------------|------|----------|------|-------|----------|------|------|----------|-----|
| | I | Leads II | III | I | Leads II | III | I | Leads II | III |
| 7713 | -0 6 | -0 2 | -2 5 | + 6 | +3 5 | +1 5 | -1 | -0 | -0 |
| 7665 | 0 | -2 | -7 | +10 | +4 | +3 | -2 | -0 | -0 |
| 7684 | -0 2 | -0 2 | -3 5 | + 7 | +5 | +2 | 0 | -0 | -0 |
| 7634 | 0 | -0 | -2 | + 2 | +2 5 | +2 | 0 | -0 | -0 |
| 7586 | 0 | -0 | -4 | + 4 5 | +4 | +3 | -0 2 | -0 | -0 |
| 7587 | 0 | -0 | -2 5 | + 5 | +3 | +2 5 | -2 2 | -0 5 | -0 |
| 7434 | -0 1 | -0 1 | -2 | + 5 | +5 | +2 5 | -2 5 | -1 | -0 |
| 7460 | 0 | -0 | -2 2 | + 9 | +5 5 | +3 | -2 | -0 | -0 |
| 7400 | 0 | -0 1 | -3 3 | + 9 | +9 5 | +5 | -3 | -0 | -0 |
| 7292 | -0 1 | -0 3 | -3 5 | + 7 | +7 5 | +2 5 | 0 | -0 | -0 |
| 7086 | -0 2 | -1 5 | -3 5 | + 9 5 | +8 | +1 | 0 | -0 | -0 |
| 7114 | -0 2 | -1 | -3 | + 8 | +6 | +1 | 0 | -0 | -0 |
| 7063 | -1 | -1 | -5 | +10 | +8 | +4 | 0 | -0 | -0 |
| 7064 | -0 6 | -0 | -4 2 | + 6 5 | +4 | +4 | -2 5 | -0 | -0 |
| 6865 | 0 | -0 | -4 | + 4 | +2 | +5 5 | -4 | -2 | -0 |
| 6728 | -0 2 | -0 | -2 | + 5 | +3 2 | +3 | -0 4 | -0 | -0 |
| 6801 | 0 | -0 | -2 2 | + 5 2 | +4 | +4 2 | -1 | -0 | -0 |
| 6816 | -0 2 | -2 6 | -6 | + 5 5 | +9 | +2 2 | 0 | -1 5 | -0 |
| 6824 | 0 | -0 5 | -2 | + 6 | +3 5 | +4 | -6 | -1 2 | -0 |
| 6834 | 0 | -0 | -6 | + 8 | +4 | +1 5 | -1 | -1 2 | -0 |

It appears evident from the data given that the Q-waves in the three leads do *not* correspond in time. In other words Q in these cases is not identical in time with Q₁ and Q₂ but represents a summation of the time represented by these deflections with varying amounts of the time taken by R₁ and R₂. Thus, in 30 of the 50 records studied (60 per cent) Q corresponded in time with parts of R₁ or R₂ in addition to Q₁ or Q₂ (see table 4). In 20 (40 per cent) Q occupied more or less accurately the same time interval as that occupied by R₁ or R₂ (see table 5). In *none* of these electrocardiograms did Q occupy the same time interval as that occupied by Q₁ and Q₂. The larger Q₁ became, the less did it agree, as far as timing was concerned, with Q₁ and Q₂ and the more with R₁ and R₂. (See figure 4.)

Figures 2 and 3 illustrate the two types of large Q₁ described above and represented in tables 4 and 5 respectively.

DISCUSSION

The data presented indicate that the Q-wave may be a physiological entity, in the sense that it may represent a fairly definite time interval and the activation of particular parts of the ventricle, only in normal ventriculograms. In abnormal ventriculograms the Q-wave represents markedly different time parts—both in the different leads of a single electrocardiogram and in different electrocardiograms. In the light of this finding it appears to us wrong to speak of Q, or of the initial deflection of the Q-R-S complex, or even of the Q of a definite lead, such as Q₁, as representative of activity in different portions of the ventricle. Since different Q₁'s can occupy grossly different time divisions of the ventriculogram they can, it seems to us, represent activity in different parts of the ventricle.

There appears to be, instead of one, three possible types of Q₁ waves, as follows:

- 1 Those that correspond in time with Q₁ and Q₂,
- 2 Those that correspond in time to Q₁ and part of R₁,
- 3 Those that correspond in time, more or less accurately with R₁.

A study of tables 4 and 5 in accordance with this division shows that none of the large Q₁ waves are of type 1, most are of type 2, and many are of type 3. In other words, the large Q₁ waves are not comparable with the normal Q₁ wave which belongs to the first type. Figure 1 illustrates Q₁ waves of the first type described, figure 2 illustrates the second type, and figure 3 the third type.

It appears clear that the large Q₁ wave, which corresponds with part or all of R₁, cannot be produced by the mechanism which causes the small normal Q-wave. The theories of Lewis² and Wilson³ of the causation of the normal Q-wave apply at most to only part of the large Q-wave. Several authors have undertaken, nevertheless, to explain the large Q-wave

by these theories. Paidee,¹ for example, quoted Lewis'⁴ concept of the normal Q-wave to support a belief that the large Q₁ represented activity in the right ventricle.

Recently Fenichel and Kugell⁵ have attempted a correlation of large Q-waves with pathological observations. They assume that they are referring to a more or less definite time part when they speak of the large Q-wave and conclude that it is caused by disturbance in the intraventricular septum—chiefly in the left half, posteriorly. We have shown that a large

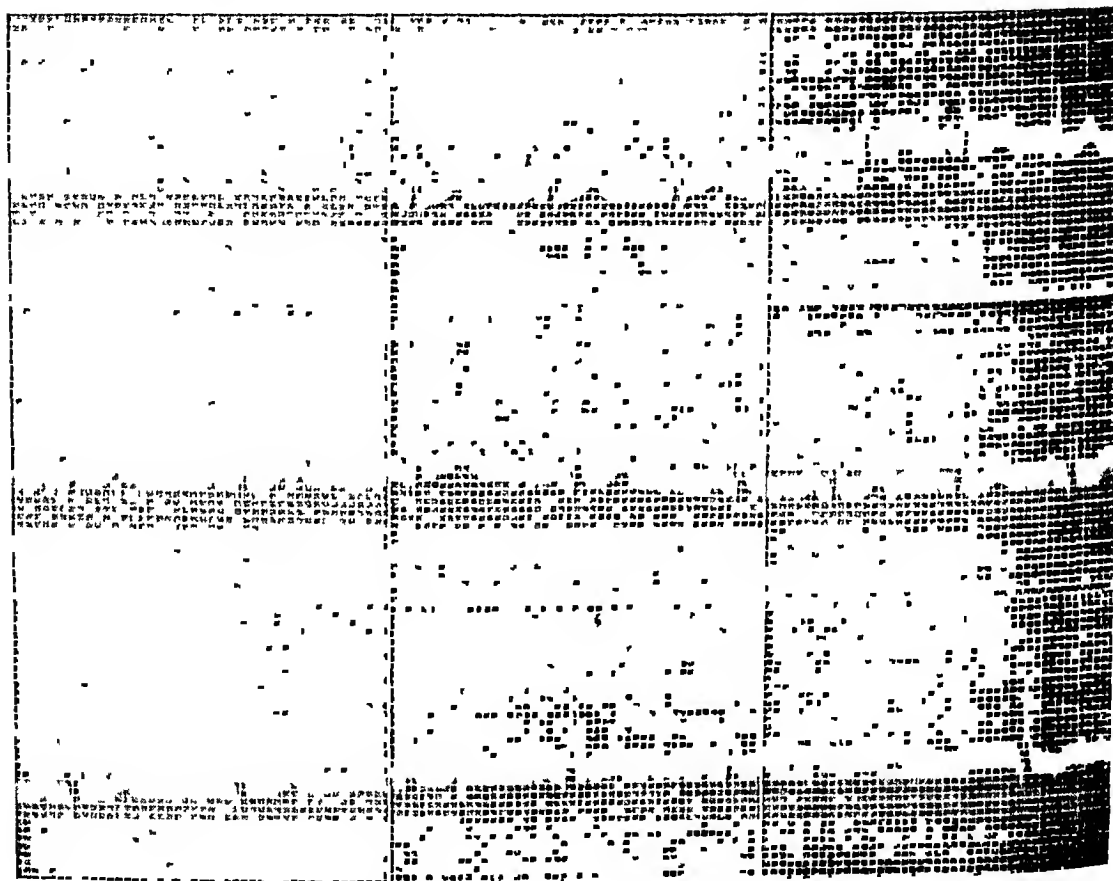


FIG. 1 Small Q₃'s which correspond in time with Q₁ and Q₂

Q₁ corresponds in time with all or part of R₁ and R₂. To accept Fenichel and Kugell's explanation of a large Q₁, one would have to conclude that R₁ and R₂ in these electrocardiograms, similarly, are, at least in part, due to septal disturbance. One would then have to explain the absence of suitable electrocardiographic representation for the rest of the ventricle. Fenichel and Kugell offer no such explanation, nor for the reduction in the size of R₃ as Q₁ gets larger, or for the usual absence of S₃ in records of the large Q₃ type. It appears to us that septal disturbances may cause changes in the initial time part of some abnormal ventriculograms, but that they

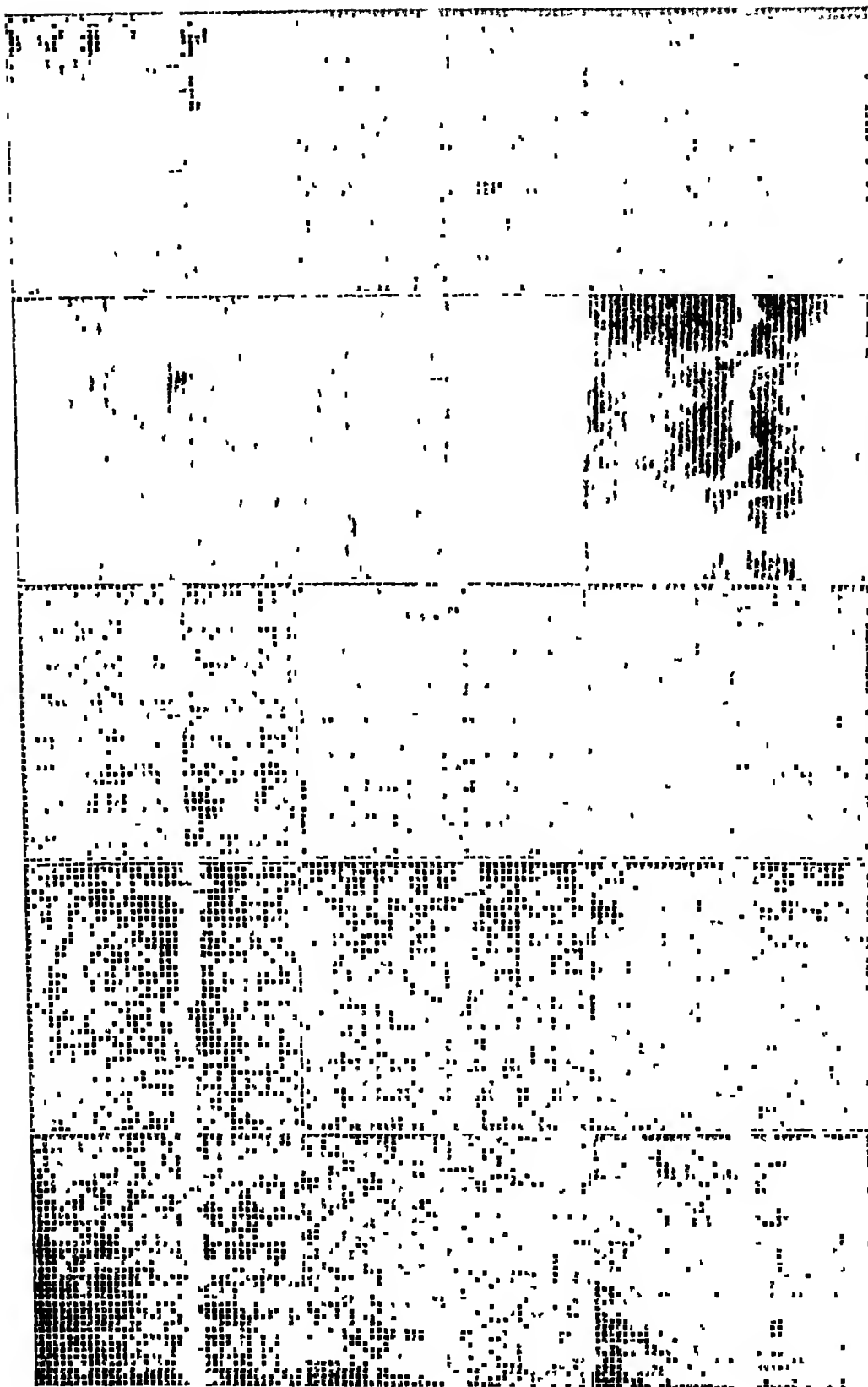


FIG 2 Illustrating large Q_3 s which correspond in time with Q_1 plus part of R_1

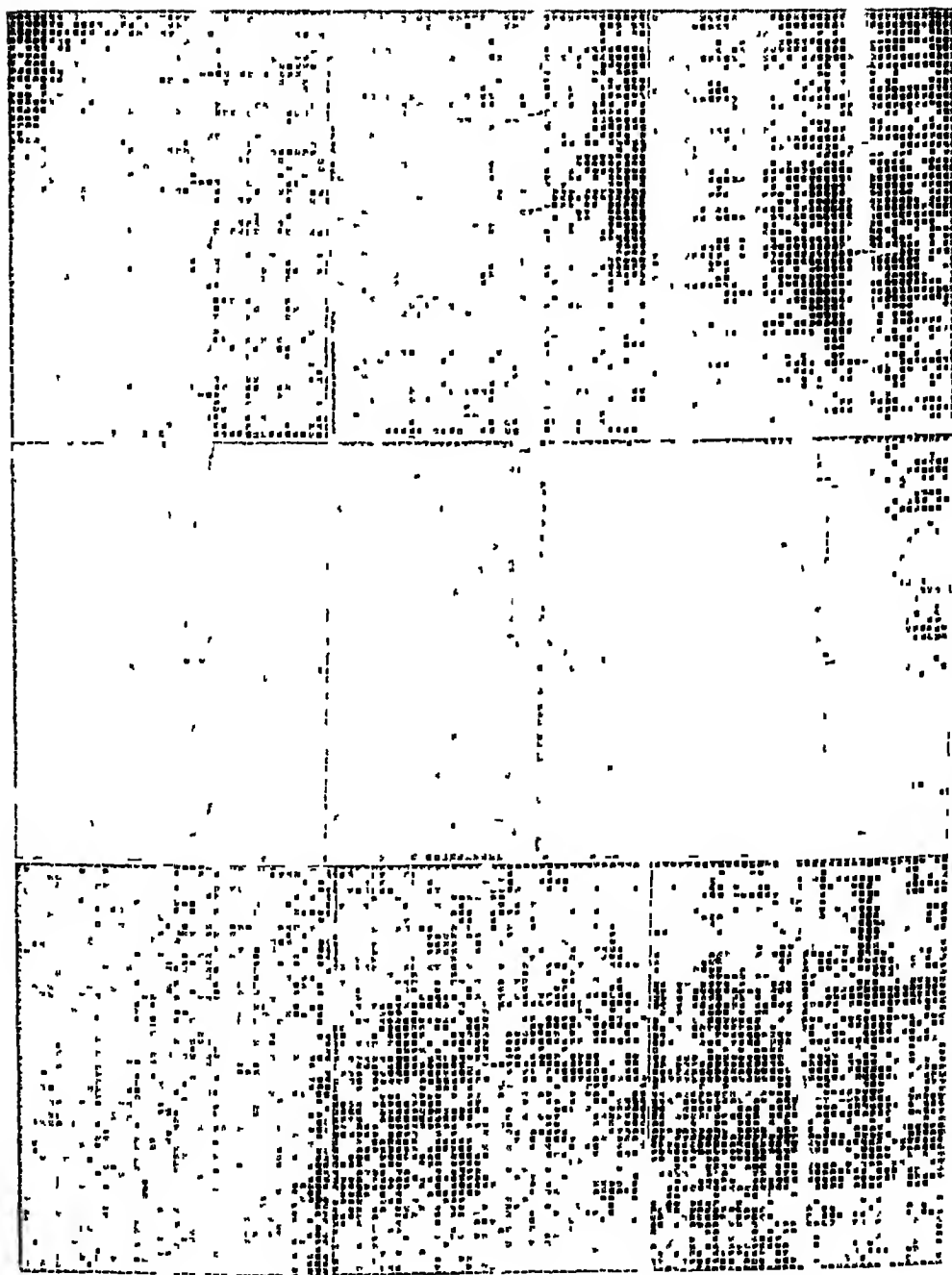


Fig 3 Large Q_i 's which correspond in time with R_i

cannot by themselves explain those large Q_1 's which represent almost all of the activation phase of the ventriculogram (figure 3). In the hearts studied by Fenchel and Kugell, pathological changes were not limited to the septum and it appears to us probable that pathologic lesions in the ventricular wall, rather than in the septum, produced most of the large Q_1 waves in their series.

We wish to emphasize at this point that in records of the large Q_1 type, the *entire* Q - R - S , not Q alone, is altered in rather a characteristic way, i.e., as Q_1 becomes larger, R_1 becomes smaller and S_1 disappears. (See figure 4.) (At times in these records P_1 becomes inverted¹⁷.) These facts should be borne in mind in the following discussion. They suggest a change in the spread of the excitation wave in the ventricle as a whole, rather than in a limited portion of it. Figure 4, an indifferent series of electrocardiograms with large Q_1 waves, indicates that the *larger* Q_1 *becomes*, the *smaller* does R_1 *become* and the more does Q_1 correspond in time with R_1 . The Q/R ratio of the first electrocardiogram presented, in which Q_1 is normal, is practically the reverse of the Q/R ratio in the last electrocardiogram of figure 4, in which Q_1 is large. The fact that Pardee¹ found S_1 so infrequently associated with a large Q_1 is explainable, at least in part, by the fact that in many tracings with a large Q_1 , the small R_1 present corresponds in time with S_1 and represents the same ventricular activity that S_1 represents. A study of the changes that respiration causes in the relation of the Q , R and S waves, one to another suggests an interdependence so that when one wave varies, the others also change in characteristic fashion. (See figure 5.) The same relationship is found when a large Q is produced in pregnancy.^{1,6}

We regard as significant the work of Meek and Wilson⁷ who produced a large Q_1 by rotation of a dog's heart about its longitudinal axis to the left and a large Q_1 by rotation of the heart about its longitudinal axis to the right. Their observations agree with the clinical finding of a large Q in the A-P lead in normal individuals when the right arm electrode is placed anteriorly and the left arm electrode posteriorly—an arrangement which represents a relative rotation of Lead I 90° to the left (around a longitudinal axis) or of the heart 90° to the right. (See figure 6.) As the right exploring electrode is shifted toward the left, the Q -wave becomes larger and the R relatively smaller. This is illustrated in figure 17B (precordial leads) of Wilson, et al.,⁸ as well as in our figure 6B.

We believe that the assumption that a large Q is caused chiefly by rotation of the ventricular electrical axis about a longitudinal axis can explain all the known facts about a *large* Q . Such rotation could be caused

- (a) By mechanical factors that change the position of the heart,
- (b) By a change in the position of the leads, causing a relative rotation of the heart,
- (c) By damage to part of the ventricular musculature with collapse, the contraction of scar tissue or the dilatation of a damaged area,
- (d) By thickening of one part of the ventricular musculature



FIG. 4. Shows that as Q_2 gets larger it corresponds more with R_1 and less with Q_1 . Note the occasional inversion of P in these tracings.

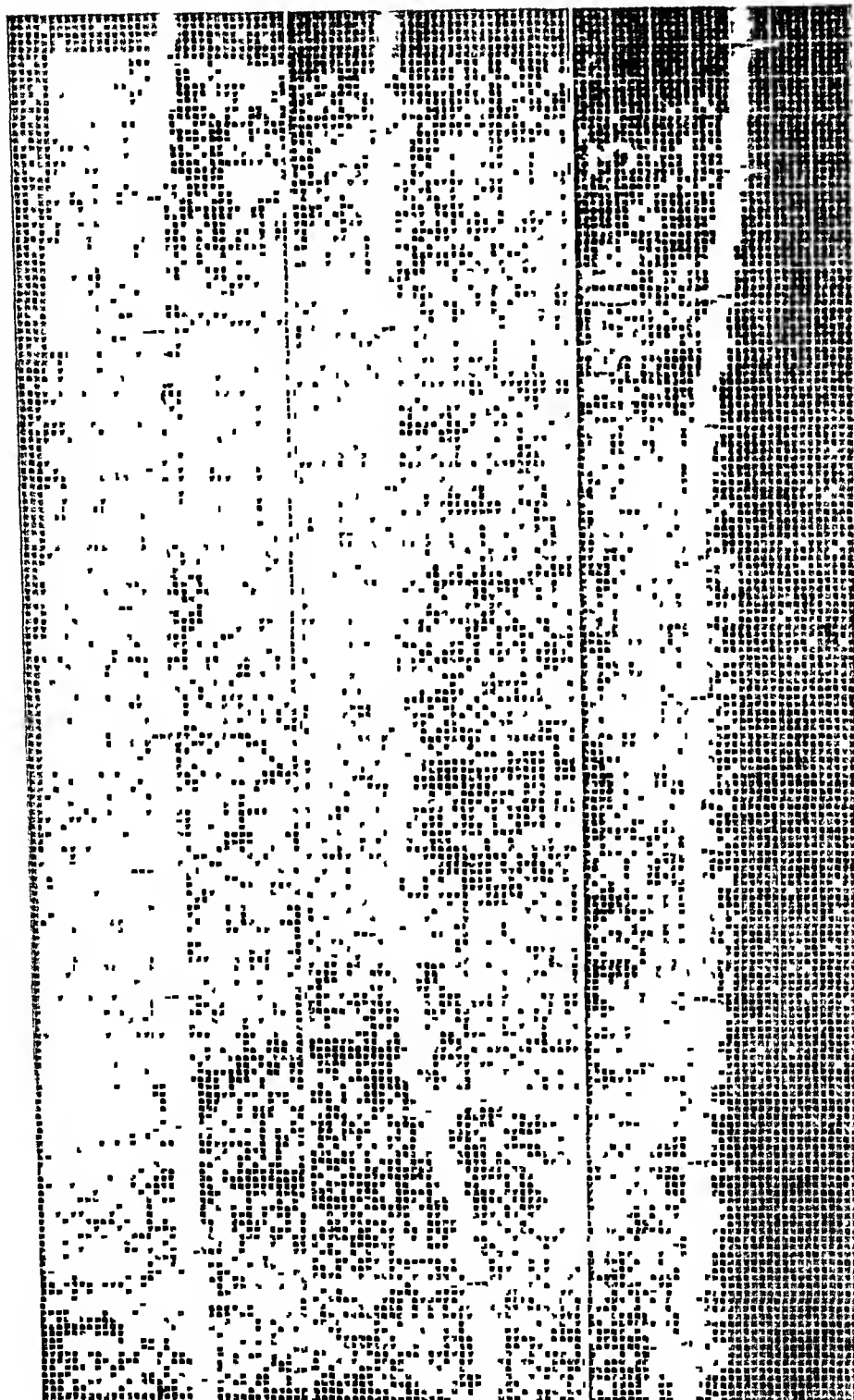


FIG 5 This is the third lead of a curve showing the changes in the relationship of the Q and R in the respiratory phases. The three strips are continuous

Pardee¹ and others^{8, 9, 10, 11} found a large Q, most commonly associated with coronary artery disease—cases of hypertension, arteriosclerosis or aortitis. In this type of case the outstanding pathology consists of damage to the ventricular musculature that is more or less diffuse but is most marked

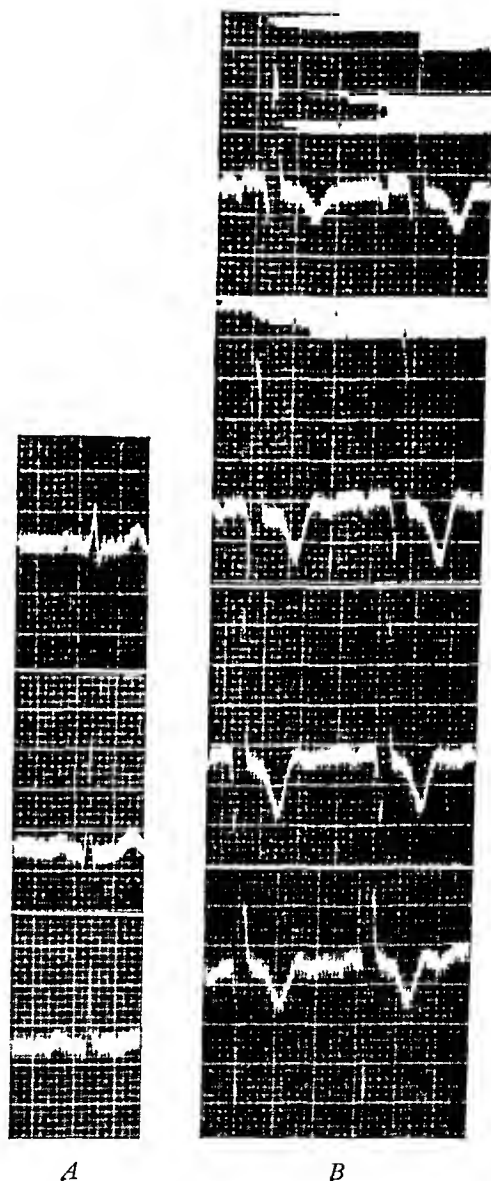


FIG 6 (A) The three conventional leads of a normal individual, from whom the posterior-anterior leads (B) were taken (B) Anterior-posterior leads, with the left electrode placed slightly to the left of the spine, at the mid-scapula level, and the right arm electrode in 1 placed to the right of the right border of the sternum in the fourth space, 2—at the left border of the sternum, 3—at the midclavicular line, left, 4—in the anterior axillary fold at the same level. Note the increasing depth of the Q-wave and the changing relationship of the Q to the R as the exploring electrode is moved to the left, being the equivalent of an increasing rotation of the heart to the right on its longitudinal axis

in the left ventricle—degeneration due to ischemia, or infarction with an inflammatory reaction and connective tissue replacement. It does not appear to be far fetched to postulate that collapse of necrotic heart muscle, traction due to scar tissue or dilatation of weakened areas may be causes for a relative rotation of the electrical axis about a longitudinal axis. That large Q's are occasionally found in normal adults, and with greater frequency in normal infants (Kumbhaar and Jenks¹² and Seham¹³), and in pregnant women¹ appears consistent with our thesis. The relative frequency of a large Q₁ in cases of pericarditis¹ is also explicable by the assumption of a longitudinal rotation of the electrical axis.

The application of this theory to the findings of Wilson and his co-workers⁸ suggests that the large Q₁ found with infarction of the anterior and lateral wall of the left ventricle, secondary to occlusion of the descending branch of the left coronary artery, may be the result of a collapse of the necrotic tissue with a rotation of the electrical axis about a longitudinal axis to the right. Similarly, collapse of a dead area on the posterior wall (caused by occlusion of the circumflex branch of the left coronary artery) might produce a large Q by a rotation of the electrical axis about a longitudinal axis to the left. Exceptions to the rule could be the result of dilatation of weakened areas, rather than collapse, with ensuing longitudinal rotation in the opposite direction. A clear illustration of this is given in figure 7. This figure shows a definite Q₁ T₁ group. Clinically the patient presented definite signs and roentgenologic findings of an aneurysmal dilatation of an acute myomalacia which could very well have caused a relative rotation of the left ventricle about a longitudinal axis to the right (Shookhoff and Douglas¹⁴).

In considering the significance of a large Q₃ it is interesting to recall the history of our interpretation of a large S₃. At first the name *left ventricular hypertrophy* was given. When it was realized that a deep S₃ was not always associated with hypertrophy of the left ventricle, the name *left ventricular preponderance*, and when the inaccuracy of the latter became evident, the present name—*left axis deviation*—came into use. It has been shown that a large Q₃ may be found with normal

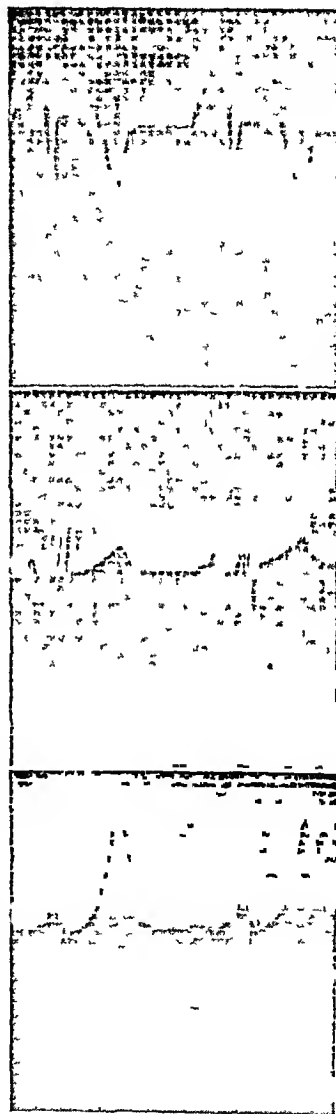


FIG 7 A case of aneurysmal dilatation of an acute myomalacia. Note the Q₁ T₁ type of ventriculogram. Note also the inverted P₂. Taken 14 days after occlusion.

adult hearts, with infants' hearts, in pregnancy, and with coronary artery disease. We believe that the common factor represented is a rotation of the electrical axis about its longitudinal axis—in some cases produced by extra cardiac causes and in some cases produced by changes intrinsic in the ventricle. Other electrocardiographic changes and clinical findings must be sought as clues to the causation of any particular Q . (The same applies to Q_1 .)

SUMMARY AND CONCLUSIONS

1 In normal ventriculograms Q_1 , Q_2 and Q_3 correspond in time with reasonable accuracy. In normal ventriculograms, therefore, the term " Q " represents a physiological entity and determination of its significance can be attempted.

2 In ventriculograms of the large Q_3 type, Q_3 does *not* correspond in time with Q_1 or Q_2 . The time represented by Q_3 in 50 of these tracings was in *no* case identical with that occupied by Q_1 and Q_2 . In *most* of these tracings part of Q_3 corresponded in time with parts of R_1 and R_2 . In *many* of these tracings Q_2 corresponded more or less accurately in time with R_1 or R_2 .

3 Evidence was offered to show that a large Q_1 is usually associated with characteristic changes in R and S—suggesting an alteration in the ventricle as a whole, rather than in one part of it in these cases.

4 It was suggested that a large Q might be indicative of a rotation of the ventricular electrical axis around a longitudinal axis, rotation to the left producing a large Q_1 , and rotation to the right a large Q_3 .

5 Such rotation could be the result (a) of mechanical factors changing the position of the ventricle, (b) of a change in the position of the leads, causing a relative rotation of the heart, (c) of damage to one part of the ventricular musculature with collapse, the contraction of scar tissue, or dilatation of the damaged area, (d) thickening of one part of the ventricular musculature.

6 In a particular electrocardiogram there is no more reason for considering a large Q_3 indicative of coronary artery or myocardial disease than there is for regarding a deep S_3 as indicative of hypertrophy of the left ventricle. We believe that a large Q_3 , like a deep S_3 , is caused by a change in the relative position of ventricular musculature—for which many different causes may be responsible.

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CERTAIN BASES OF PHYSICAL THERAPY *

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DURING the past year it has fallen to my lot to become particularly interested in physical therapy. What I shall have to say is addressed not to expert physical therapists but to practicing physicians who, like myself, have had heretofore but a desultory interest in the subject and while not deeming the value of empiricism in therapeutic methods, would still wish to know something of the underlying physiological factors that may have been determined.

Although physical therapy may have been over-exploited here and there during the past several years, one gets the impression that it is much more widely neglected to the great detriment of many patients who are badly in need of it. The Council on Physical Therapy of the American Medical Association is doing a valuable work in disseminating useful information on this subject and in protecting the profession against misleading and deceptive advertising. They have wisely emphasized the point that among the physical methods of treatment the fundamentals are massage, active and passive exercise, muscle training exercises and the application of heat. As a corollary to this statement one may add that a well trained, skilful technician, intelligently directed, is of more value than much costly apparatus.

In addition to manual methods, what external stimuli do we find employed? Perhaps it will serve a unifying purpose to glance for a moment at the range of electromagnetic rays, the source of so many marvels in the physical world of today. On the left of the range are the shortest waves, the so-called cosmic rays, then successively with increasing wave lengths, the gamma rays, the x-rays, and after a relatively unknown gap the ultra-violet or chemical rays, the narrow band of visible light (from 360 to 760 millimikrons), followed by the broad band of infra-red or heat rays, the Hertzian rays that include the shorter and the longer radio waves, and finally at the extreme right of the range, the alternating current waves. You will note that many of our physical therapy modalities have their bases in electro-magnetic rays of one or another wave length, and it is safe to say that the potentialities of further discoveries in this electro-magnetic range seem infinite.

In the use of physical methods one may wish to affect many different tissues and parts of the body, but the most exposed and the most accessible of them all is the skin with its immediately subjacent tissues. We have all been taught, but we are prone to forget, that the skin is not merely an integument, a covering for the body, but a complex tissue with many func-

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934

tions Let us pass some of them in review First, there is the integument, a physical barrier to the outside world Second, the sebaceous glands Third, the blood vessels with their remarkable reactions in maintaining and regulating body temperature and in defense against injury Fourth, the lymph vessels Fifth, the sweat glands with their service in temperature regulation and in excretion Sixth, the function of insensible perspiration, also of value in temperature regulation Seventh, the nerves and nerve endings, the sources of sensory impressions and of reflex activities Eighth, other metabolic or chemical factors under which we may mention (a) resorption, a factor of little importance in the human skin, (b) pigment formation, (c) the histamine-like substance postulated by Lewis, (d) ergosterol, which is changed by ultra-violet irradiation to viosterol, with the production of vitamin D, (e) the high potential of tissue immunity emphasized by Kahn who finds that the skin possesses a specific reacting capacity for antigens more than ten times as great as the reaction capacities of muscle, of brain, or of plasma

The skin then is a complex structure capable of a variety of reactions to stimuli both from without and from within The vascular mechanisms are particularly intriguing and have been studied by many physiologists, including Sir Thomas Lewis, who found that numerous and widely different forms of stimulation yield in common three distinct events, these are (a) a primary and local dilatation of the minute vessels of the skin, (b) a widespread dilatation of the neighboring strong arterioles brought about entirely through a local nervous reflex, and (c) locally increased permeability of the vessel wall In explanation of this complex mechanism he postulates the release of a histamine-like substance and considers it a normal metabolite that is responsible for many of the normal vascular reactions as well as those occurring under conditions of stress In the light of such researches it seems entirely probable that many of the reactions of the skin and other tissues to physical therapeutic procedures are really defense reactions on the part of tissues to outside agencies and are non-specific as far as the particular therapeutic method is concerned There are of course specific responses as illustrated by the difference in the skin reactions to heat rays and to ultra-violet rays, and by the striking difference in reflex activities following the applications of cold and of heat All these responses, specific and non-specific, may be considered defense mechanisms and whenever the defense reaction is favorable to the condition under treatment, the therapeutic method is useful

HEAT

As many of the procedures in physical therapy involve the use of heat, we may well consider next some of the results of local and of general heat that have been determined by physiological experiments Let us recall that although we customarily speak of the body temperature as 37°C (98.6°

F), the temperatures in different parts of the body are not the same. There are many temperature gradients that may be modified by the application of additional heat.

The heat capacity of the tissues is high (0.8) so that considerable heat may be absorbed before a change in temperature can be measured. This capacity varies also with different tissues. The conductivity of heat in the tissues is made quite variable by the marked changes in vascularity. When the skin and subcutaneous fatty tissues are cold and the vessels contracted, the conductivity is relatively poor and less heat is given off from the surface. When, on the other hand, the tissues are warm and the vascular channels dilated, the conductivity is markedly increased.

Heat may, of course, be applied by different methods, namely, by conduction as with the hot bath or a hot water bottle, by convection as from hot air, by radiation as from the sun or therapeutic lamps, and by conversion whereby electrical energy is converted into heat within the tissues of the body as by diathermy. A favorite method for superficial heating is the use of radiant energy, the most valuable wave lengths for this purpose being those of visible light and of the infra-red. The wave length with the greatest penetrating power through the tissues is given as 1150 millimikrons, that lies in the near infra-red. This wave length is best obtained by the use of a gas filled, tungsten filament bulb.

Owing to the slow penetration of heat by conduction when it is applied to the surface, to the relatively poor penetration of the infra-red rays, and to the efficiency of the local vascular protective mechanism, it is now generally believed that the use of diathermy is the method of choice in attempting to heat the deeper tissues in most conditions where this is desired. Even here, although the heat is generated within the tissues themselves, it is rapidly dissipated, no great storage of heat occurs and there is no striking rise of temperature. But after all, the chief purpose in the local use of heat in physical therapy is usually not so much the production of an increase in temperature per se as an acceleration of the circulation, an increase in blood flow, which must occur in a part where there is a large additional amount of heat to be dissipated. Hence the absence of any striking rise in temperature is not necessarily an indication that a useful purpose is not served by the treatment.

In view of the importance of an active circulation for the dissipation of heat within the tissues and for their protection from damaging degrees of heat, one must needs be careful in its application to parts where the local circulation is notably defective. Here we have an explanation of the well founded dread of heat that many physicians have in the treatment of gangrene and even of the lesser manifestations of peripheral vascular disease. This danger would seem to be obviated by the method of controlled heat suggested by STARR, who finds that the optimal temperature in such cases is usually that of the normal skin temperature of the part.

The Effect of Heat on the Circulation This very important effect of heat is exerted both directly upon the vessel walls and reflexly through the vasomotor nerves. Heat produces vasodilatation and cold, vasoconstriction. Not only is the effect a local one but through the reflex activities distant parts of the vascular tree may be affected as has been demonstrated definitely by Lewis and others.

There are marked variations in the blood flow as the result of heat or of cold. The local circulatory rate in the arm in an arm bath has been measured and recorded. At 32°C (approximately the normal temperature) the flow of blood was 13 cc per 100 cc of tissue per minute. At 26°C the flow was 5.5 cc of blood per 100 cc of tissue per minute. At 46°C the flow was 26 cc of blood per 100 cc of tissue per minute.

Heat also produces a marked increase in the transudation of fluid from the blood vessels and hence in the formation of lymph. When these vascular changes are widespread as in a warm bath, for example, there occur definite readjustments in the fluid balance with increased formation of lymph in the skin and subcutaneous tissues but, in the splanchnic area vasoconstriction, diminished capillary tension and increased absorption of water. Similarly, cold applications to the skin may result in vasodilatation of internal vascular beds and a consequent diuresis.

Effects of Heat on the Blood When the blood is heated locally there are marked changes in its physical chemistry with a shift toward the acid side as is illustrated in the following experimental record. The blood was obtained from an arm vein after the arm had been placed in a water bath at the different temperatures. At 33°C (91.4°F), pH 7.45, pOH 6.3, CO_2 tension 35 mm, O_2 saturation 70 to 90 per cent, O_2 tension 45 to 55 mm. At 40°C (104°F) pH 7.3 to 7.4, pOH 6.2, CO_2 tension 45 mm, O_2 saturation 90 per cent +, O_2 tension 70 to 95 mm.

The Effect of Heat on Metabolism The metabolism of the tissues is definitely increased by heat. As tested upon an isolated organ, as in the perfused heart, it is estimated that the metabolism increases two or three times with a rise of 10°C .

There is an interesting experiment in the study of cyanosis in the forearm produced by stasis due to a constricting band on the upper arm. In a water bath at 31°C (87.8°F) cyanosis was obvious in three minutes, at 42°C (107.6°F) cyanosis occurred in one minute, at 15°C (59°F) no cyanosis occurred in 15 minutes. From this experiment it is obvious that the usage of oxygen was markedly affected by the changes in temperature.

Hitherto we have been dealing with the local application of heat. As you well know, by more general heat applications or by the prevention of heat loss, a rise in the general body temperature can be induced. The complex changes that are brought about by elevating the body temperature may be summarized as follows. Increased circulatory rate, rise in blood volume, marked increase in the ventilation rate, fall in alveolar CO_2 tension,

rise in oxygen consumption, increased metabolism, and changes in the pH of the blood and urine to the alkaline side. Clinical work indicates a definite change of tone in the autonomic nervous system.

EXERCISE

To quote Bair: "Muscular exercise is accompanied by the coordination and integration of many functions. The participation of higher nerve centers, and the increased respiration and circulation are as much a part of exertion as the muscular contraction itself." During the contractile phase of muscular activity there is a breaking down of glycogen into lactic acid and during the recovery phase the lactic acid is re-converted into glycogen. "Due to the accumulation of acids there is during the contractile phase a diminution of alkalinity, not only in the muscles but also in the whole body, a change which is corrected during the recovery phase."

MASSAGE

With massage, on the other hand, there are no such complicated readjustments as in active exercise, nor do we find metabolic changes like those associated with the use of heat. There does occur, even with light stroking, a non-specific reaction on the part of the minute vessels of the skin, and with deep massage doubtless of those in the muscles also. Capillary dilatation has been observed microscopically by Pemberton and others following light massage. There is further the mechanical assistance to the venous blood flow and also the lymph flow with presumably in this way an aid in the removal of waste products from the tissues affected. Probably in this way, too, is brought about the increase in the red blood cells and hemoglobin of the circulating blood as well as the increased oxygen capacity that has been noted following massage. In spite of the paucity of physiological data there is no doubt from the empirical standpoint of the value of massage. One of the most ancient, it is also one of the most valuable measures in the realm of physical therapy. Of great value to many chronic invalids who must, for one reason or another, remain in bed for periods of weeks, it is really indispensable in the rehabilitation phase of the treatment of injuries and of many diseases of the bones, joints and muscles. Yet so great is the neglect of this useful procedure in many localities that patients must go to the osteopath or to the chiropractor in order to receive its benefits.

THE ULTRA-VIOLET RAY

The treatment of rickets, infantile tetany and osteomalacia by means of the ultra-violet ray rests upon abundant biochemical studies. It is generally agreed that the favorable effects are due to photochemical reactions resulting from absorption of the rays and the prevailing opinion at present favors the view that the sterol in the skin is rendered photoactive by radia-

tion It has been shown that irradiated animal or human skin is antirachitic and that this action is independent of the nervous or circulatory systems

The use of ultra-violet rays or of heliotherapy in the treatment of extrapulmonary forms of tuberculosis, of erysipelas, and other superficial infections rests chiefly upon an empirical basis

In conclusion, in this brief and quite incomplete discussion of certain bases of physical therapy it is suggested that they are chiefly defense mechanisms of the tissues in response to external stimuli and that the most valuable of these mechanisms from the therapeutic standpoint would seem to be those of the vascular system with increased flow of blood through the part treated

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THE DIABETIC CHILD

ETIOLOGIC FACTORS

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HEREDITY

Heredity is the most important factor in the causation of diabetes in children. In a study of literature from all over the world, which includes 1,418 cases of diabetes in children, the disease was hereditary in 30.8 per cent (table 1). In reality this percentage is higher, for the longer the

TABLE I
Heredity in Children

| Author | Number of Cases | Heredity | | Familial Hereditary Per cent |
|----------------|-----------------|-------------------|---------------------|------------------------------|
| | | Familial Per cent | Hereditary Per cent | |
| Collens-Grazel | 10 | | | 50 |
| Freise-Jahr | 60 | 10 | 1.6 | 11.6 |
| Holt | 50 | | | 30 |
| John | 214 | 4.6 | 14 | 18.7 |
| Joslin-White | 750 | | | 40 |
| Lion-Moreau | 100 | | | 23 |
| Ladd | 35 | | 37 | 37 |
| Priesel-Wagner | 108 | | | 27 |
| Toverud | 47 | | | 17 |
| Smyth | 31 | | | 54 |
| Total | 1418 | | Average | 30.8 |

diabetic children live the more diabetes is discovered in their families. The true percentage on this basis is probably somewhere near 40 per cent.

In my own series of 214 cases of diabetes in children and adolescents, the proportion in which heredity played a part was about equal in the boys and the girls, namely 18.7 per cent (table 2). There was an interesting contrast, however, in the hereditary factor among Gentile and Jewish children. In the Gentile children, there was a family history of diabetes in 17.9 per cent, whereas in the Jewish children it amounted to 30 per cent (table 2). Unfortunately I have no figures to offer for the incidence of childhood diabetes in the two races.

P. White in a series of 533 diabetic children, 45 of whom were Jewish, found the hereditary incidence to be 44 per cent in the Jewish group, and Priesel and Wagner in Vienna, in a series of 108 children, 29 of whom were Jewish, found 43 per cent with a familial history among the Jews, as contrasted with 21 per cent in the Gentile group (table 3).

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934

TABLE II
Heredity (John)

| Total number of diabetic children 214 | | Boys 111, girls 103 | | | |
|---------------------------------------|-----------------|---------------------|-----------------|-------------|-------------------|
| | Familial | | Hereditary | | |
| | Number Cases | Per cent | Number Cases | Per cent | Total Per cent |
| Boys | 5 | 4.5 | 17 | 15.0 | 19.5 |
| Girls | 5 | 4.8 | 13 | 12.6 | 17.4 |
| Total | 10 | 4.6 | 30 | 13.8 | 18.9 |

Relation in Heredity in the Jewish and the Gentile Children

| | Familial | | Hereditary | | Total Per cent |
|-------------|-----------------|-------------|-----------------|-------------|-------------------|
| | Number Cases | Per cent | Number Cases | Per cent | |
| 20 Jewish | | | 6 | 30 | 30 |
| 194 Gentile | 5 | 2.5 | 30 | 15.4 | 17.9 |

TABLE III
Heredity Relation in the Jewish and the Gentile Children

| Author | Total No Cases | Gentile | | Jewish | |
|--------------------|-------------------|-----------------|----------------------|-----------------|----------------------|
| | | Number Cases | Heredity Per cent | Number Cases | Heredity Per cent |
| John | 214 | 194 | 17.9 | 20 | 30 |
| White | 533 | 488 | ? | 45 | 44 |
| Priesel- Wagner | 108 | 78 | 21 | 30 | 43 |
| Average | | | 19.4 | | 39 |

It has been pointed out by many authors that diabetes is transmitted as a recessive character according to the Mendelian law. This is shown graphically in figure 1, in which the black dots represent the diabetics, the clear rings the non-diabetics, and the half clear rings the non-diabetics with a hereditary background. The first diagram shows that when a diabetic marries a diabetic all the children will be diabetic, the second that in a union of a diabetic with a nondiabetic with a hereditary background, one-half of the children will be diabetic. The third diagram shows that when a nondiabetic with a hereditary background marries a nondiabetic of the same type, one-fourth of the children will be diabetic, and the fourth shows that when a diabetic marries a normal person with no familial background of diabetes, no children will be diabetic.

This then gives one a practical working basis for prognosis and indicates the practical and moral responsibility which we physicians face in advising a diabetic concerning marriage. If the birth of future diabetics

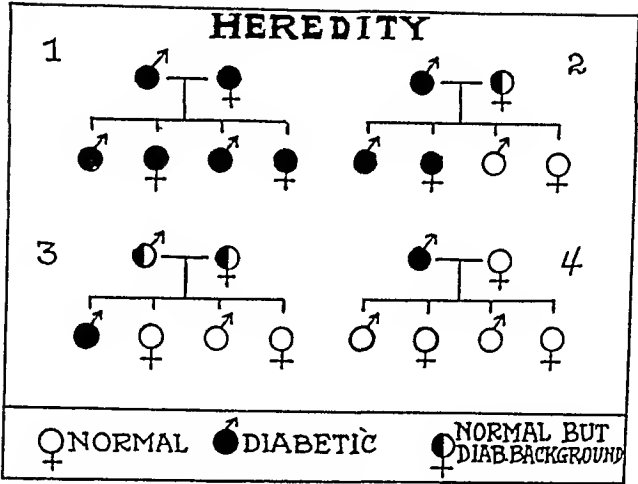


FIG 1 Heredity in diabetes Illustration of the Mendelian recessive

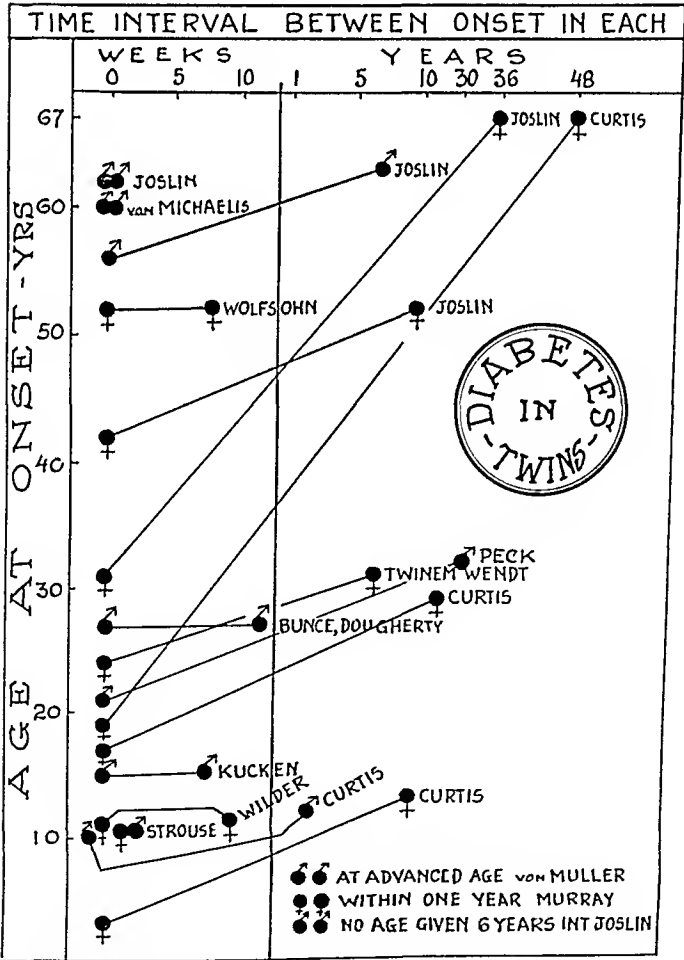


FIG 2 Twins with diabetes The sex, the interval of time between the onset in each pair and the author who reported them

is to be prevented the other partner must not only be nondiabetic, but also have a family history free from diabetes

Figure 2 presents a study of diabetic twins arranged according to the time interval between the onset of diabetes in each pair in a total of 19 pairs of twins reported in the literature. In three pairs the onset was simultaneous, and in four pairs within 12 weeks of each other. Such data present instructive and presumptive evidence of the hereditary nature of diabetes.

INFLCTION

Infections play a considerable part in the production of diabetes in children. When one considers the havoc which an infection plays even in a mild case of diabetes, one can readily understand why an infection might precipitate diabetes in a diabetotrophic child, that is, one with a tendency toward diabetes. Figure 3 illustrates the damage caused by infection in

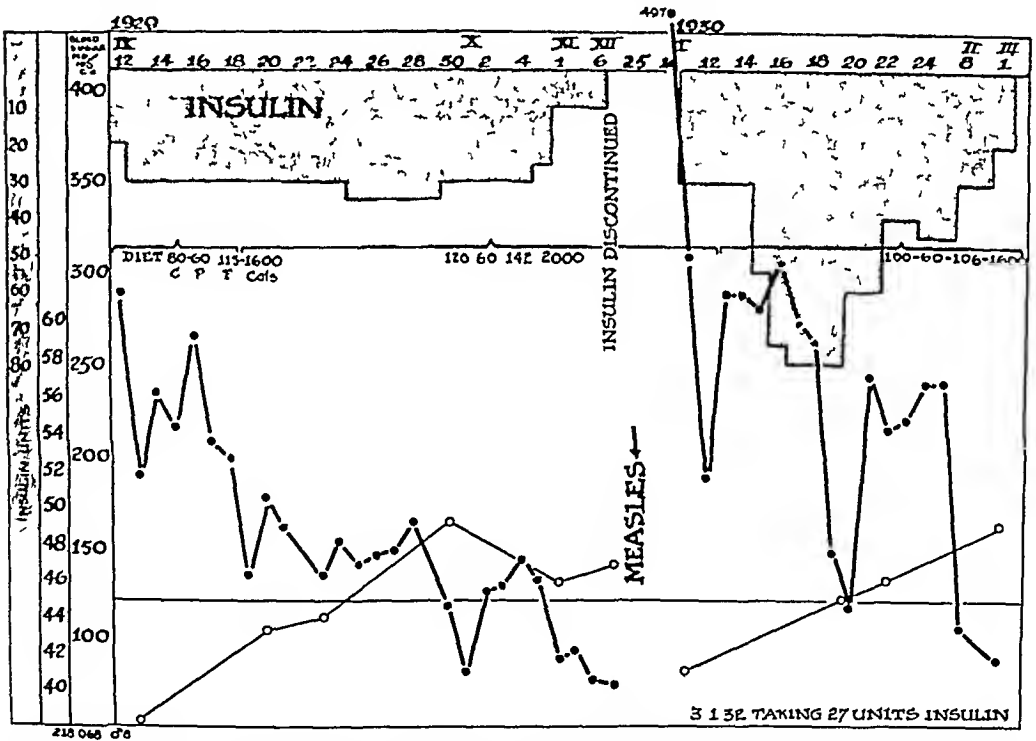


FIG 3 Infection and the part it plays in a child who was a mild diabetic Note the permanent loss of previous tolerance

the case of a little boy, aged four years, whose diabetes had improved under adequate treatment so that all insulin could be discontinued. He presented a normal fasting, noon and evening blood sugar and was sugar-free on diet alone on repeated examinations. He contracted measles and, as the physician who was attending him in the small town where he lived did not appreciate the change in the situation and the need for reinstating insulin during the course of the infection, when I saw him a few weeks later his blood sugar was almost 500 mg per cent and he displayed signs of severe

acidosis Insulin had to be reinstated in large quantities and to this day he is taking large quantities of insulin, because the faulty management during the infection wrought permanent damage which apparently is irreversible This case shows the importance of proper management during acute infection in a diabetic child

There is some evidence that in all acute infections, even in normal persons, there is decreased sugar tolerance If the reserve insulogenic function is sufficient, it is not exhausted even by repeated infections But a lesser reserve is more easily exhausted and diabetes may be thus precipitated Unfortunately we usually see these children at the time when diabetes develops and we know little or nothing of their background, that is, whether that child had diminished insulogenic function before the infection or whether this was normal This phase of the problem of diabetes will have to be explored if we expect to arrive at any sort of logical solution, which will aid in the prevention of diabetes Prevention, after all, is the only worthwhile goal, for we cannot cure diabetes, but with increased knowledge we should be able to reduce its incidence

That infection does play a part in the development of diabetes in children can be deduced from figure 4 These data on a group of my own series

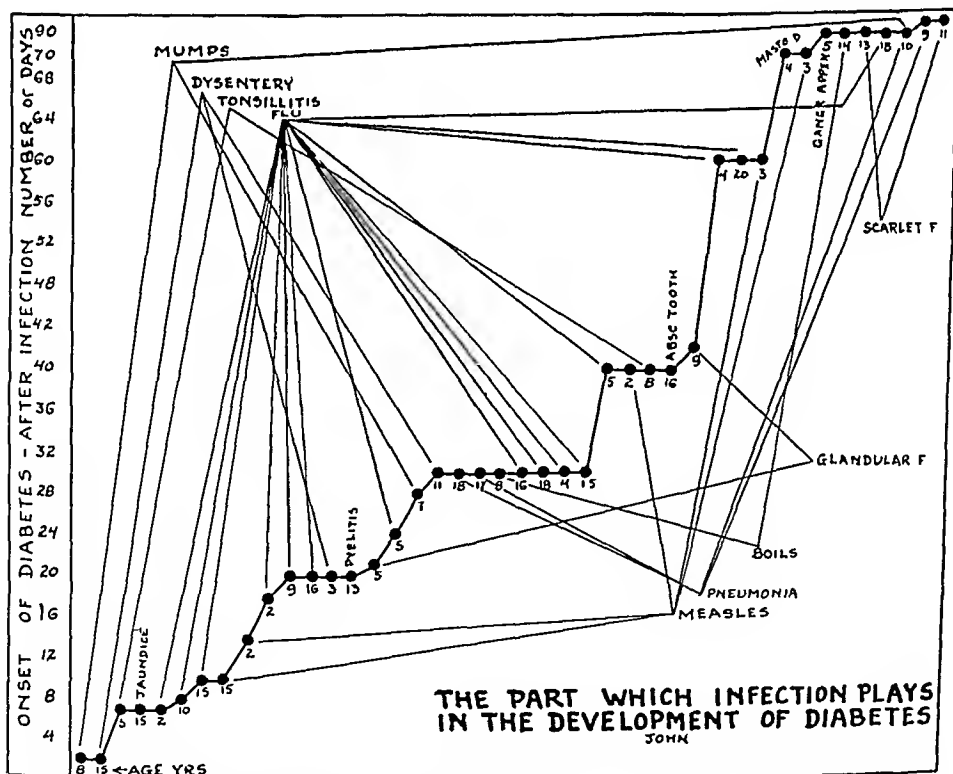


FIG 4 The onset of diabetes in a group of 34 children from my own series following the various infections and the length of time intervening between the infection and the onset of diabetes

of cases show the relation of the onset of diabetes to preceding infection. The time between the infection and the onset of diabetes often is very short, in some instances only two days, in nine cases 10 days and in 15 cases 20 days. Such evidence can not be disregarded. In table 4 I have gathered

TABLE IV
Onset of Diabetes in Children Following Infections

| | Number of days after infection when diabetes was discovered | | | | | | Not Stated | Total |
|---------------------|--|-------|-------|----|----|----|---------------|-------|
| | 1-10 | 11-20 | 21-30 | 38 | 41 | 58 | | |
| Mumps | 2 | 1 | 1 | | | | 24 | 28 |
| Influenza | 4 | 3 | 5 | 1 | | 2 | 1 | 16 |
| Measles | 1 | 1 | 1 | 1 | | 1 | 1 | 6 |
| Dysentery | 1 | 1 | 1 | | | | 3 | 6 |
| Pneumonia | | | 2 | | | | 1 | 3 |
| Int. toxemia | | | | | | | 3 | 3 |
| Boils | 1 | | 1 | | | | | 2 |
| Tonsillitis | 1 | | | 1 | | | | 2 |
| Nephritis | | | | | | | 2 | 2 |
| Glandular fever | | | 1 | | 1 | | | 2 |
| Jaundice | 1 | | | | | | | 1 |
| Septic endoc | | | | | | | 1 | 1 |
| Poliomyelitis | | | 1 | | | | | 1 |
| Abscessed teeth | | | | 1 | | | | 1 |
| Infectious diseases | | | | | | | 23 | 23 |
| Pyelitis | | 1 | | | | | | 1 |
| Total | 11 | 7 | 13 | 4 | 1 | 3 | 59 | 98 |

from the literature cases of diabetes in children following an infection and have added similar cases from my own series. I do not know the background of these children, that is, whether they were perfectly normal or whether they were children with a diabetic tendency, a diminished insulogenic function, the "Minderwertigkeit" of the Germans. I suspect the latter, but I cannot be sure. Priscilla White¹ in her book on "Diabetes in Children and Adolescence" states that "infections play no rôle or are of little or no significance in the production of diabetes in children." This statement certainly is contrary to my own experience.

A. Jones² in England called attention to the fact that following an influenza epidemic, the incidence of diabetes increased. Lierle and Potter³ of Iowa City, in their study of the diabetic child, state "we have observed that low grade and early diabetic conditions are recognized first during acute colds and tonsillitis." Von Noorden⁴ also believes that diabetes does develop following infection. Hirschfeld⁵ has expressed the view that an infection such as angina or flu causes damage to the pancreas and can bring about diabetes. Freise and Jahr⁶ state that nearly three-fourths of their diabetic children developed diabetes shortly after acute infections. Similar statements have been made by von Starck,⁷ Weiland,⁸ et cetera.

Pancreatitis follows at times as a complication of parotitis. It is perhaps more frequent than the literature would indicate, for not all cases are reported. In 1900, Jacob⁹ reported a case in a child, aged 10 years. In that same year Priestley¹⁰ reported two cases, one in a boy aged 14 and the other in a man of 25. Auché¹¹ in 1905 reported two cases in boys 9 and 12 years of age. Biahdy and Scheffel,¹² Gentry,¹³ Stevens¹⁶ and others have reported additional cases. Farnam¹⁴ collected from the literature 119 cases of pancreatitis complicating mumps and added one of her own. Barbieri¹⁷ tells of a boy six years old with mumps during an epidemic. Six days after the onset of the symptoms he complained of a continuous pain above the umbilicus which radiated around the right side to the right lumbar region. The pain continued, next day he vomited and developed diarrhea. Two days later he had a voracious appetite and a great thirst but everything he ate he vomited an hour later. He drank two liters of water a day. The urine was loaded with sugar. The symptoms subsided gradually and disappeared after 15 days and by that time the urine was sugar-free.

That infection produces a marked rise of blood sugar even in young infants, or produces a diabetic type of curve was shown by Fritz Goetzky¹⁷. In an infant three and a half months old with fever and bilateral bronchopneumonia, the fasting blood sugar was 79, but after the administration of 10 gm of glucose in tea, the blood sugar taken after three hours was still 264 mg per cent. In another infant, two months old, with fever and hydration, the fasting blood sugar was 120 when the fever subsided on the third day, but when 12 gm of glucose were given in tea the blood sugar rose to 178 at the end of the second hour and at the end of the fourth hour it was still 134. Lauritzen¹⁸ recommended as a prophylactic step in diabetes the testing of children's tolerance by the production of glycosuria *et amylo*.

MacLean and Sullivan¹⁹ studied the tolerance of 97 children from three months to five years of age with various diseases. Seventeen infants with infections in the acute stage did not reveal any consistent change in the carbohydrate metabolism. Ten showed normal, six increased, one decreased tolerance.

This I think is quite suggestive. Out of the 17 children but one showed a decreased tolerance. Why? Was the infection due to a more toxic organism or was the infant one with a smaller insulogenic reserve? This is the type of child to follow carefully through succeeding years, for if the decreased sugar tolerance was the result of lessened insulogenic reserve this child should later in life develop diabetes. This sort of study forms the foundation on which we can build and eventually hope to reach the point of better understanding of the functional background of diabetes. It may lead nowhere and again it may shed much light on this problem.

According to Williams and Dick²⁰ there is a lowering of dextrose tolerance in acute infections and it may last for several months.

Labbe and Boulin¹ stress the fact that during infection glycemia is increased and the glycemie curve is four times longer, with the maximum hyperglycemia increased by 50 per cent. This reveals an important change of the sugar regulating balance. Alimentary glycosuria was noted in 75 per cent of their series. The disturbance of the glucose regulation did not parallel the gravity of the infection. The impairment of glucose balance sometimes becomes more pronounced during convalescence and persists for weeks or even months after recovery from the infection. There was no sign of an insufficient functioning of the liver. "It is possible," they say, "that recurrences of this transient disturbance of glucose balance creates a true diabetes more frequently than hitherto believed."

As an explanation for the hyperglycemia during infection, five possibilities present themselves: (1) reduced insulin output, (2) inability of the liver and the muscles to store glycogen readily, (3) the action of insulin may be interfered with as it is in acidosis and fevers, (4) the nervous control mechanism may not be functioning properly, and (5) there may be an increased output of adrenalin which increases the hyperglycemia. Goetzky¹⁷ and Czeiny think that the second factor is of prime importance. Hahn,²² Offenbacher²³ and John²⁴ think number one is the most probable factor. Various authors have expressed the opinion that the third factor is of major significance. All five may be important and at different times the various factors may be involved in various proportions.

Root and Warren²⁵ state "The character of the lesions of the islands of Langerhans suggests a toxic origin acting over a long period of time."

I have always felt that if liver damage were of prime importance hyperglycemia would be encountered more frequently, furthermore, in patients with marked cirrhosis of the liver, there is no hyperglycemia. Waikany²⁶ studied the level of fasting blood sugar in a three and a half year old child with cirrhosis of the liver. The fasting blood sugars were normal, 60-106. A glucose tolerance test, using 30 gm of glucose, produced a normal curve.

Were the insulogenic function involved, the hyperglycemia should be in direct proportion to the insulogenic reserve of the individual. Even here one will not get a clear picture as the problem is a complex one for there can be a marked insulogenic derangement of a temporary nature, which, once relieved, will quickly return to good function, and if not relieved and if prolonged it may go on to a frank diabetic state. That this occurs I²⁴ have shown in previous publications.

In figure 5 are shown the blood sugar changes during and after pneumonia in a child three years old. I have constructed these curves from Kohn and Felshin's²⁶ figures. Note the marked rise and slow fall of blood sugar during the crisis and the subsequent drop of the curve after the infection has subsided. In the first curve starvation tends to distort the curve toward the diabetic side. In diabetics during an infection the

insulin requirement is greater and we speak of this as inactivation of insulin. There is also an increased adrenalin output during infection. We might well be dealing with a similar problem in regard to the endogenous insulin in such a case of pneumonia. The important thing is that in most cases the decreased glucose tolerance is but temporary, but occasionally it

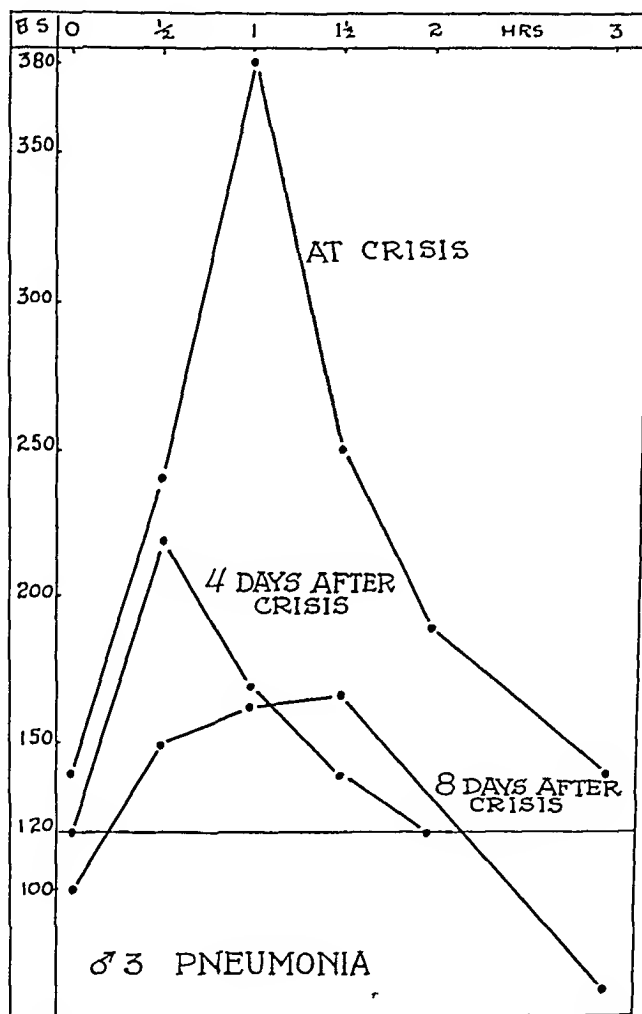


FIG 5 Glucose tolerance tests in a three year old infant with pneumonia at crisis, four days after crisis and eight days after crisis

becomes permanent which means that the patient has diabetes. Are these exceptions due to a less efficient insulogenic function with which the child started life? Or is it a certain type of action of bacteria and their toxins on the pancreas? I have no answer to offer.

I have followed out this problem a bit further in a comparative study of glucose tolerance tests on children and adults with various affections

The findings were quite striking (Figure 6) In obesity and hyperthyroidism, for instance, adults show diabetic curves about three times as often as do children In glycosuria, rheumatism and hypopituitarism the incidence is about the same In hypopituitary disease there is an increased sugar tolerance Sixty-six per cent of cases of glycosuria are nondiabetic Rheumatic conditions and chronic infections carry a heavy

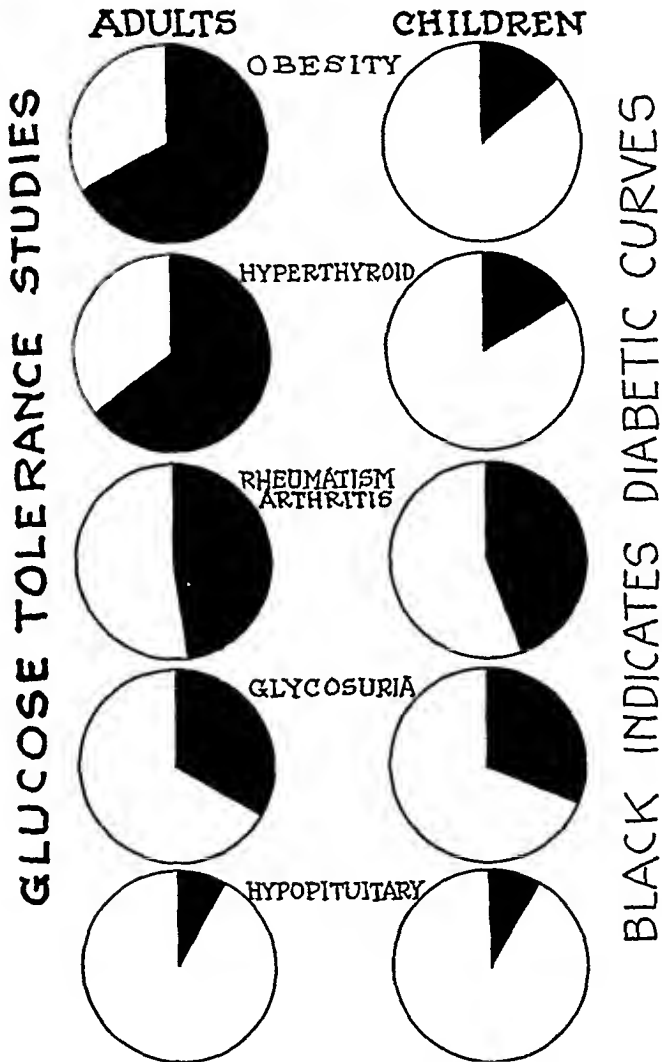


FIG 6 Comparative studies of glucose tolerance tests in adults and children afflicted with the same condition

incidence of diabetic curves both in children and adults Hyperthyroidism does not disturb the carbohydrate tolerance of the child nearly so much as it does that of the adult, the same can be stated regarding obesity Here then we have the difference, functional I think, between the child and the adult The child is a better physiological unit on the whole than the adult who has been harassed by infections, wear and tear, dietary abuses et

eetia for decades and has thus exhausted much of his reserve. Any superposed strain on such a background produces a different picture from that where the background is intact.

OBESITY

A series of 1306 cases of adiposity was reported in 1925 by Anders and Jameson.²⁷ In this series the authors found 119 or 9.1 per cent of the patients had diabetes. The general incidence of diabetes is at most 2 per cent so that the increase in the incidence of diabetes as judged from this series is about 500 per cent. In my series of diabetics, 76 per cent of the patients were more than 10 per cent overweight at some time during their lives. The threat of diabetes, then, is very real to the adult who is obese.

The question of obesity in children fortunately does not present such a serious outlook, but Mouriquand²⁸ in 1920 warned us to be on the alert to detect incipient obesity in children of the obese, the diabetic, the arthritic and the gouty parents. He says that nearly all of his patients who had early inherited obesity developed diabetes before the age of 40, but that when the inherited obesity did not develop until later in life only 50 per cent became diabetic, and in acquired obesity only 15 per cent developed diabetes.

In my glucose tolerance studies on obese children and adults it was shown that the children had three times the resistance to diabetes that the adults had. This is well illustrated in the case reported in 1925 by McKinley²⁹ of a girl 18 years of age who had endogenous obesity and weighed 346 pounds. Her blood sugar and glucose tolerance test were normal. On the other hand Wagner³⁰ reported the case of an obese girl, 12 years of age, who was diabetic in the presence of definite hypothyroidism which usually is accompanied by an increased tolerance. Lindblom³¹ reports a boy, 16 years old, with hypothyroidism and severe diabetes who died in coma.

However, on the whole, the problem of obesity in children plays but a minor rôle as can be gleaned from figure 7, which shows the incidence of obesity in the various decades in a series of 528 of my cases which I analyzed some time previously. In the first decade it amounts to but 1 per cent, though the second decade already shows an increase.

Nevertheless, one should look upon an obese child with suspicion and settle the problem regarding its carbohydrate metabolism. The treatment of obesity in children depends upon the underlying cause for it, which often is of endocrine origin.

ARTERIOSCLEROSIS

While arteriosclerosis frequently accompanies diabetes in the older patient and probably plays an important part as an etiologic factor, it is almost a negligible factor in the young. Pearl Zeek,³² who searched the literature over the last 100 years, found but 98 cases of juvenile arteriosclerosis.

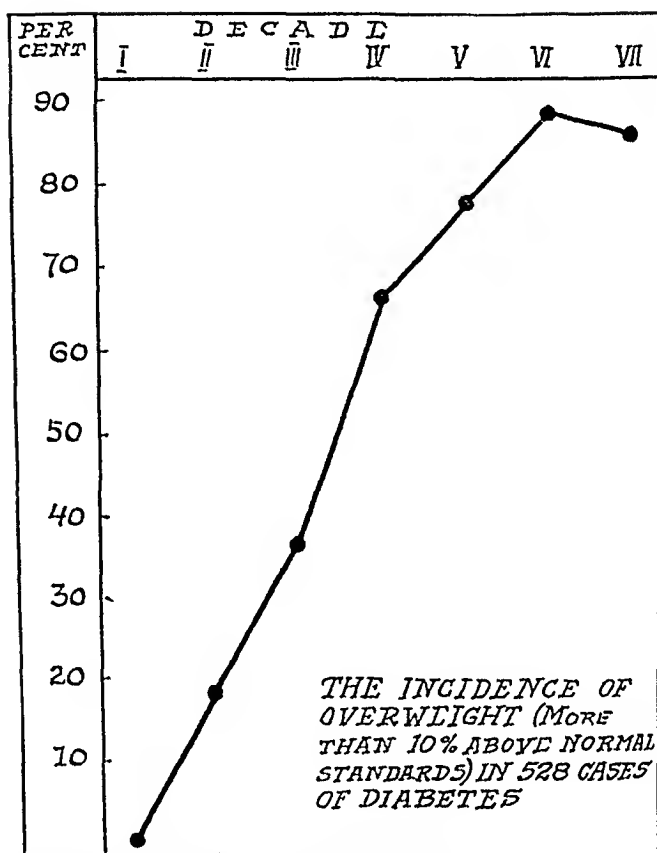


FIG 7 The incidence of overweight in 528 diabetes from my own series in the various decades

excluding those due to luetic infections and, as far as could be determined, none had diabetes. Nephritis, lues, and tuberculosis are factors which are most frequently associated with premature arteriosclerosis. Arteriosclerosis, however, does appear in the diabetic child after he has had diabetes for a number of years much more frequently than it does in the nondiabetic child.

HYPERTHYROIDISM

That hyperthyroidism in children is not a rarity is a well known fact. In table 5 I have gathered 285 cases reported in the literature.

In a study of 9,000 hyperthyroid adults³³ I found 6.88 per cent with a derangement of carbohydrate metabolism which manifested itself by a nonphysiological hyperglycemia either with or without glycosuria. This derangement during the acute stage of hyperthyroidism often is considerable. Thus in a series of 239 glucose tolerance tests on adult patients with hyperthyroidism, 64 per cent gave a curve like that of diabetes. I have considered this as a lack of physiological response. Either the glycogen storage function is at fault, or the nervous control mechanism which regulates the insulin output is interfered with, or else there is an abnormal

TABLE V
TOXIC GOITER in Children

| Author | Year | Number of exophthalmic goiters in children 14 or less | Boys | Girls | Total Exophthalmic Goiters |
|------------|---------|---|------|-------|----------------------------------|
| Helmholz | 1921-26 | 30 | 4 | 26 | 3,432 |
| Sattler | 1909 | 184 | 39 | 144 | 3,477 |
| Lewis | 1905-13 | 5 | 0 | 5 | 1,512 |
| Dinsmore | 1926 | 48 | 8 | 40 | |
| White | 1912 | 1 newborn | | | |
| Klaus | 1914 | 1 infant 9 mos | | | |
| Klein | 1922 | 3 | | | |
| Wynter | 1911 | 1 | | | |
| Pritchard | 1910 | 1 | | | |
| Woodward | 1914 | 1 | | | |
| Roillet | 1914 | 1 | | | |
| Else Peden | 1925 | 18 | | | |
| Lahey | | 1 (3 yrs) | | | |
| Total | | 285 | | | |

stimulation of the adrenals producing hyperglycemia, or a temporarily lessened insulogenic function, or the insulin does not act properly as is the case during infections. Any one or all of these factors are possibly of importance but which one predominates and to what extent we do not know.

In a series of 9,000 cases of hyperthyroidism I analyzed 620 cases of glycosuria carefully. During the derangement of the carbohydrate metabolism these patients were closely watched and received adequate insulin for their protection, but not all of them regained their normal insulogenic function. One hundred and eighty-six patients remained diabetic and receive treatment for diabetes to this date. Thus the actual incidence of diabetes in hyperthyroidism in my series was 21 per cent with protection. What it would have been without such protection I do not know, but I venture to say that it would have been considerably higher. But even so it is about 100 per cent more than the general incidence of diabetes.

When we come to study the problem of hyperthyroidism in the child we see a different picture. Figure 6 shows that diabetic curves occur in cases of juvenile hyperthyroidism only about one-fourth as frequently as they do in the hyperthyroidism in adults. Apparently the greater reserve or flexibility in the young can withstand a grave metabolic derangement and still right itself. In my own series of children with hyperthyroidism who were protected during and after the acute stage of hyperthyroidism none developed a frank and lasting diabetes. This is in sharp contrast with the adult group. I have under my care, however, two children with diabetes who had some derangement of their carbohydrate metabolism during the acute stage of hyperthyroidism. Both were subjected to thyroidectomy. Both were told by the surgeon to forget about their blood sugar and both returned later with frank diabetes and are under treatment.

to this date Had these children been protected for six months or a year, they might not be diabetic today

On the whole, hyperthyroidism plays but an insignificant part as an etiologic factor in the production of diabetes in children When abnormalities in the carbohydrate metabolism are found, they should be controlled thoroughly by a liberal diet and a sufficient amount of insulin to insure proper utilization of the food Sugar free urine together with normal blood sugar should be attained and maintained long after operation until a complete restoration of function has taken place Only thus can diabetes from this source be prevented

LULS

All authors are agreed that luetic infections are of no significance as an etiologic factor in diabetes Joslin and the European authors express themselves alike in this respect and in my own series I found none in whom syphilis could have been a predisposing factor Lasalle¹ studied a group of four diabetic infants from poor families and he stated that syphilis was a probable cause of the diabetic condition While lues does play a small part in the production of diabetes in adults or at least accompanies it, in children it is a negligible factor

SUMMARY

1 The average percentage of cases of diabetes in children in which heredity was an etiologic factor in a series of 1,413 cases from the literature was 30.8 per cent In my series of 214 cases of diabetes in children the hereditary incidence was 18.7 per cent In Jewish children there was a hereditary influence in 39 per cent as contrasted with 19.4 per cent in Gentile children In my own series, the incidence in Jewish children was 30 per cent and 17.9 per cent in the Gentile group Diabetes apparently is a recessive character according to the hereditary laws of Mendel Heredity in 19 pairs of twins is analyzed according to the time interval between the onset of diabetes in each pair In three pairs it was simultaneous

2 Infection in diabetic children requires close and adequate management if the child is to emerge from it without further impairment of sugar tolerance In my own series of diabetic children, in nine cases, or 4.2 per cent, the onset of diabetes followed within 10 days after the infection, in six cases, or 2.8 per cent, the onset was within 20 days, in 45 cases, or 21 per cent, the onset was within 60 days The onset of diabetes may follow any acute infection and every child should have a weekly urine examination until there is ample evidence that sugar is being utilized normally In the early stages of diabetes, the process is to a certain extent still a reversible one whereas at a later stage no repair is possible

3 Comparative studies of glucose tolerance tests in children and in adults having various affections present a striking and an interesting con-

trast between the two groups in obesity and hyperthyroidism. In rheumatism and glycosuria and hypopituitarism they are practically alike.

4 Obesity in the adult presents a high incidence of diabetes, as much as five times the general incidence of the disease. Obesity in children does not present a major etiologic problem.

5 Arteriosclerosis is not a causative factor of juvenile diabetes.

6 Hyperthyroidism plays an insignificant rôle as a causative factor in diabetes in children as contrasted with the same condition in adults. However, nonphysiological hyperglycemia during active hyperthyroidism should not be disregarded and the child should be given protection during this period until the carbohydrate metabolism has returned to its normal function.

7 Lues can be disregarded as a causative factor of diabetes in children.

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PSYCHOLOGICAL CONSIDERATIONS IN THE TREATMENT OF THE NEUROSES *

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THERE can be little question but that a very large proportion of those who consult their physicians for other than purely surgical, acute infectious or obstetrical conditions are suffering from some form of neurosis, which, in many cases, is psychogenic in origin. The *function* of some organ or organs is at fault while the organ itself is in no way diseased. The diagnosis of such a condition as some form of organic disease is one of the commonest errors in diagnosis met with today. The battle-scarred abdominal wall of one who has submitted to one surgical procedure after another in seeking a cure is altogether too commonly seen, nor is it surprising that this should be the case. Ever since the beginnings of scientific medicine in the seventeenth century, and particularly during the last hundred years, the main emphasis in medical education and practice has been on the physical side of man and but little attention has been given to the mental. Most of those who are now practicing medicine were well trained in anatomy, physiology, biological chemistry, pathology and bacteriology but comparatively few received any instruction to speak of in psychology. In the clinical field, too, almost the entire emphasis up until a few years ago was placed on organic disease, and many medical schools have offered courses in clinical psychiatry for the first time during the past half a dozen years. What wonder, therefore, that physicians so largely seek to find a physical basis for all disease states and fail to consider a possible disorder of the psyche. Sir William Osler counseled us always to bear syphilis in mind when making a diagnosis but it is even more true of a neurosis that it can masquerade in the guise of almost any organic disease. To mistake a neurosis for organic disease has the most serious consequences for the patient, as the major surgical or prolonged medical treatment of a neurotic is much more harmful in its consequences for him than for the emotionally stable individual. To differentiate between a functional and an organic condition is often a major test of the diagnostic acumen of the physician.

But when the diagnosis of a neurosis has been made, how should the individual be treated? Plato said, "As you ought not to attempt to cure the eyes without the head or the head without the body, so neither ought you to attempt to cure the body without the mind and this is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole, which ought to be studied also." The individual must be studied as a whole, both body and mind, in order to determine

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the genesis of his neurotic symptoms. A careful search must be made to find out what, if any, organic disease is present, but the patient's personality must be studied also.

Often a very superficial knowledge of the patient is sufficient, and simple suggestions for rest, a change of scene, slight dietary modifications and sedatives may work wonders. But in other cases, much deeper studies of the patient may be necessary. Herbert Spencer said, "Life is a series of internal adjustments to external environment" and the neurotic person is often one who fails to make the adjustments satisfactorily with resultant deep emotional disturbances which are hard to discover. The emotions are the source of a large part of man's psychic energy when his emotional life runs smoothly. But when it fails to do this and major emotional conflicts develop, the individual is apt to suffer from a neurosis. It may, therefore, be of the utmost importance to understand the emotional make-up of a patient and the way in which he reacts to his particular problems of life. This may entail a detailed survey of the patient's early education and environment, his likes and dislikes, his hopes and fears, his degree of introversion and extroversion, his sexual adjustment and other emotional reactions. One is apt to hear the remark "O! He's just a neurotic" as if a neurotic were an inferior being. This is often far from being the case and the patient is simply emotionally immature rather than inherently inferior. To discover the deep lying emotional factors in a case and then to re-educate the individual to meet his particular problems in life without the development of neurotic symptoms is both the problem and the method of successful approach for the physician. A broad understanding of human nature and some knowledge of so-called "mental mechanisms" is of the greatest help to the physician in accomplishing these aims.

The following cases are reported to show (1) how a neurosis may simulate organic disease, (2) that the causes of neuroses are often psychological, and (3) that the symptoms usually disappear if the patient's emotional conflicts can be solved. None of these patients had any organic disease which was in any way related to their neurotic disorder.

CASE I

The patient complained of intense nervousness and hoarseness. He was in a highly agitated state, could eat and sleep but little and spoke in a hoarse whisper. He had been sued for misuse of funds that had been entrusted to his care and, when called to the stand to testify in his defense, he suddenly lost his voice. The judge granted a postponement so that he could recover his voice and not have to testify under a disadvantage. The man had been receiving local treatments for his aphonia without any benefit and had finally been told that he must stand trial in spite of his physical condition. He felt confident that he could vindicate himself, and his lawyer assured him that he had nothing to worry about. But there were many things about this man's personal life which no one knew about except his opponent and he was afraid that they would come out at his trial. He was no physical coward. Powerfully built, mentally alert he had stroked his university crew and had seen four years of active service at the front during the World War as a captain in the British army. He

had been decorated more than once for bravery under fire but he could not face the possibility of losing his case in court and, with it, his reputation as an honest and highly moral man. He was told that he would not recover the use of his voice until he went through with his trial. The case was tried. The patient testified and promptly recovered his voice and usual calmness even though he was convicted.

This is a typical case of hysterical aphonia which failed to respond to local medical treatment and disappeared only when the emotional conflict which produced it was resolved. Like many of the cases of "shell shock" in the World War, the patient unconsciously developed a symptom which protected him from facing a situation of which he was afraid.

CASE II

A white woman of 33 complained of repeated convulsive seizures over a period of nine months and severe backache over a period of 10 years. She had been under various physicians' care at different times for her backache and had received but little help. Finally, 18 months before she came under observation, a suspension was done in the hope that the backache would be cured when her retroverted uterus was put in good position. The objective of the operation was attained but the backache continued. After a slow convalescence of nine months the patient was about to return to her work when she had her first convulsive seizure. Although thorough examinations of many kinds were made, no cause for the convulsions was found and the patient came to the conclusion that she was a hopeless epileptic. In spite of the fact that she had been in the hands of many physicians, none of them had taken the trouble to explore her past life beyond a few perfunctory questions.

An analysis was undertaken. Space will not permit the reporting of the progress of the case in detail but it may be summed up by saying that she had had a frightfully unhappy childhood under the domination of an unusually cruel stepmother and that this had colored her whole subsequent emotional life. As a child the patient, Cinderella-like, had been made to slave in the interests of her younger step-sisters and had been taught to believe that she should always give way for someone else. Starved while her sisters were fed plentifully, the patient stole from the pantry night after night and then cried herself to sleep thinking that she was a wicked girl. At 21 she fell in love and the world looked brighter. Her mind pictured a happy, normal existence—a home, husband, children. But the object of her affection was engaged to another girl whom he did not love. He told the patient that he would break his engagement and marry her. But the second woman was a friend of the patient's and hadn't she been brought up always to sacrifice herself for others more worthy than she? And so, in the end, she gave up the man she loved and refused to marry him. She then determined to forget him and began training to become a trained nurse. She would thus be devoting herself to the service of others who were in need. Then the backaches began. Through the medium of dreams early forgotten memories were recalled. These memories were frequently of unjust and inhuman treatment at the hands of the stepmother. Among other episodes recalled was one in which the stepmother had kicked the patient in the small of the back after a severe scolding for something the patient had not done. The helpless little girl had felt that she would have killed her had she had the means—a wicked thought and one that had to be banished from the mind of a girl with strong religious principles. Another dream dealt with a time when she was stripped and beaten across the back with a whip in the presence of her older brother. Other dreams revealed the fact that the patient was still in love with the man she had refused and whom she thought she had forgotten. And here is another example of the work of an unconscious factor. When

denied normal wifehood and parenthood, the patient had tried to do something she really did not want to do. A neurosis developed which prevented the accomplishment of this substitute existence and a symptom appeared which symbolized the cruelty of the stepmother, the cause of all her trouble, and her hatred for her.

This is another case of hysteria and one which was much more serious in every way than case 1. Even after many conferences, during which a good rapport had been established, ordinary questioning failed to bring out the essential emotional conflict because the patient herself had repressed it. It was only by the use of dream analysis that this conflict was revealed. As the patient gradually recalled early forgotten memories and changed her point of view toward her stepmother and other things, her symptoms disappeared. She is leading a normal, active life today and has not had a convulsion or a pain in the back for over four years.

CASE III

A young married woman complained of general "nervousness" and "cystitis." She had all the symptoms of this latter condition in a mild form and had been cystoscoped many times by a very capable urologist, who told her that her bladder appeared normal in every way and that he could find no reason for the frequent return of her symptoms. But although he had seen her off and on for several years, he had never inquired into her sex life beyond a few brief questions such as "is everything all right between you and your husband?", to which she responded that it was. But, as a matter of fact, it was not. This patient wanted to live, like Peter Pan, in the Never-Never Land of childhood and insisted on continuing to live with her mother after she was married. She hated children and did not want any and she grew up with the belief that all sexuality was "bestial" and "nasty" and resented the fact that she had to have intercourse. Her husband was thoughtful of her feelings and made few demands upon her. And then she discovered that every time they had coitus she developed frequent and painful urination the following day. This necessitated expensive and disagreeable treatments. Wouldn't it be better not to have intercourse so frequently? And so, once more, we find an unconsciously produced symptom helping the patient fight against an undesired adult adjustment.

The treatment of this patient was very unsatisfactory as she refused to believe that her sexual maladjustment and childishness had anything to do with her bladder trouble or general nervousness. Sick and suffering as she was, it was easier for her to live thus than to make the adjustment to her husband and to life in general which her age demanded.

CASE IV

A young married woman complained of "heart trouble," which was characterized by fainting spells. These occurred whenever she was under any emotional pressure. She had been the oldest of 10 children and the only girl. Her father was a chronic drunkard and, from a very tender age, the patient had been accustomed to hearing her drunken father making sexual demands on her mother and had lain in bed shivering with fear and disgust as she heard her mother plead with him. She had seen the economic struggle to raise a large family on a small income and had early decided that she would never marry. Then, as time passed, she became conscious of the biological urge to marry and experienced a sexual thrill in company with men. It was at about this time that she began to have fainting spells and she then thought that

she wasn't strong enough to marry and have children, although she greatly desired them. She did marry but with the fixed idea that sexual relationship was only justified in the interest of having children. At the physical consummation of her marriage, she had hysterics and the whole "honeymoon" was a nightmare. For eight years the sexual relationship between her and her husband was entirely unnatural and she would almost always have hysterics—crying, scratching and biting her husband and often ending up with a fainting spell. It was necessary for her to change her attitude toward the whole matter, a painful process for her. But she went at it in good spirit and has not fainted but once in over two years. In addition to this, she also states that she never knew what happiness was before and all her "nervousness" has ceased.

It is certainly far from true to say that all cases of nervousness have a sexual basis but many of them undoubtedly have and it was the underlying factor in this case. From an early age the patient had looked forward to the sexual act with dread and loathing and her sexual life with her husband was most abnormal. Just why her difficulties in this field produced the particular symptoms that she showed would be hard to prove but they all disappeared when her sexual life became normal.

CASE V

The patient complained of general "nervousness" and painful menstruation. In giving her history she stated that she had always had some pains with her periods but that they had been particularly severe for the past six years. She had been married about a year before and had submitted to a suspension operation in an attempt to gain relief. This had done no good and the pains had been worse, if anything, since that time. She had also found that the sexual relationship was becoming very distasteful to her and she regretted this as her husband upbraided her for not loving him as she should. His own love for her was very evidently beginning to cool. Inquiry revealed that she had been greatly tempted sexually about six years before and had several times permitted certain friends to take liberties with her that her ethical ideals condemned. She had had a terribly guilty feeling even during the period when she was permitting these intimacies and had often thought of suicide. When she married she wanted to tell her husband of her "sins" but he would not let her and she felt that she was deceiving him as to her morality. The whole subject was frankly discussed but nothing was suggested as to the effect this clearing up of a sore spot might have on her dysmenorrhea. After her next period she said, "You know, it's a funny thing but I had scarcely any pain for the first time in years." Other periods have passed and she has been almost entirely free from the severe pains that crippled her. Not only this, but she has experienced a complete change in her enjoyment of the sexual act. Naturally enough her husband has again taken interest in her and has ceased to question her love for him. No suggestion was made as to the possible relationship between the guilt feelings of six years and her menstrual and marital difficulties but the confession of those feelings and a sympathetic discussion of them has apparently cured both the troubles of the mind and body whereas surgical interference accomplished neither.

This case is of particular interest because it shows that such a common complaint as dysmenorrhea may at times be due to an emotional conflict. These conflicts so frequently have to do with sexual matters that the physician is neglecting his duty if he fails to inquire into them. This patient, like so many others, had never been asked anything about her sex life beyond a few perfunctory questions. Physicians hesitate to ask ques-

tions dealing with the sex life of their women patients and yet most women will talk about this subject very freely if their confidence is won and if they understand that this subject may have a very important bearing on their complaint

CASE VI

A married white woman of 27 presented a picture of complete nervous collapse. For four years she had gradually been getting worse until, at the time she was first seen, she was hardly able to lift her head from the pillow or take food. She had lost many pounds in weight because of her severe indigestion, she had lost all interest in things and people, including her husband and son, and was intensely irritable and on the verge of tears. She had received no help from the many physicians to whom she had gone. Most of them had told her that she was "just nervous" but one of them had gone so far as to remove her appendix, which proved to be normal in every way. It was soon established that she and her husband had been practicing coitus interruptus for many years and that she was absolutely frigid while he was very passionate. And yet these matters had never been inquired into by any of the medical consultants and the patient and her husband had not liked to ask how to prevent conception in any other way. The patient was a very immature young woman emotionally who had always been spoiled by a doting mother. She had many peculiar and childish ways of looking at the world, from the difficulties of which she had always shrunk. She and her husband were polar opposites in psychological type and could not understand each other's way of doing things. One's way of doing and looking at things seemed unreasonable to the other. Thus, in spite of a very real affection between them, there were constant misunderstandings which caused friction and unhappiness. Both the patient and her husband felt that they were drifting toward a separation in a perfectly senseless way and yet they felt powerless to help themselves. A psychological reeducation of the patient was undertaken. Gradually a more normal sexual life was established, a more mature way of looking at the problems of her life was developed and the patient and her husband reached a better understanding of each other. With these changes came a return of strength and health, interest in life and love for her husband and child. The patient now has a second child and is leading an unusually active existence.

This patient presented a typical symptom-complex of neurasthenia. She was typical of that class of patients of whom Sir James Paget said, "The patient says she cannot. Her friends say she will not. The truth is, she cannot will." Weak and sick in body, she was spiritually unhappy and her marriage was drifting rapidly upon the rocks. In handling such cases, the physician must strive not only to bring back physical health but he must also teach his patient a new way of life.

SUMMARY

In treating functional nervous cases, the physician cannot neglect to study the mind as well as the body. If he does, his patient is apt to drift away into the hands of a quack, who uses strong suggestive therapy and thus cures him temporarily. Psychotherapy must be used as well as other kinds of therapeutics in order to attain that for which the ancients strove—*mens sana in corpore sano*. This is a necessary goal for the neurotic, for a sick mind is almost certain, sooner or later, to produce a sick body.

THE MEDICAL ASPECTS OF NATIONAL HEALTH INSURANCE¹

By GRANT FLEMING, M D, *Montreal, Canada*

NATIONAL Health Insurance is a very live topic today. What is more, it is a very serious thing for the medical profession at large, if not for the public. It is well that we should understand it properly, that we should have some conception of the forms it may take, and it is further important that we, as medical men, should be prepared to advise our governments and communities as to the manner in which it should be conducted—should it eventually come to pass as a government measure or as a service to the community.

It has often been said that medicine is a science and an art. Not often enough, however, has it been pointed out that medicine is a service. Osler has expressed it well. "Medicine," he said, "arose out of the primal sympathy of man with man, out of the desire to help those in sorrow, need and sickness."

Is it not reasonable then that service should be stressed as the outstanding feature of medical practice?

Medicine is not an isolated science, it is rather an assemblage from all the sciences which contribute to an understanding of health and disease in the human being. The application of medical science during recent years has been one of the worthwhile achievements in that it has minimized human suffering, increased the average span of healthy years, and thus added materially to the sum total of man's efficiency, effectiveness and happiness.

Medicine will always be conservative, this is to be expected for it is usually influenced, if not controlled, by those who have passed that period of life which welcomes change, the leaders are experienced and know the sobering effects of personal responsibility for human life.

Change is much more gradual than it appears to be in retrospect. Sydenham (1624-1689) is known as "The English Hippocrates." This one man marks for us the break from Galen's dogmatism, which had enslaved medicine for fifteen centuries, to a philosophical consideration of disease, and his era witnessed a return to the Hippocratic method, the study of the individual patient. Sydenham marks the change, but Sydenham was, after all, only the product of his time, not the instigator of the movement. As you will recall, Boerhaave (1668-1738), at the same period, played a similar role in Holland.

¹ Delivered before the American College of Physicians, Chicago, Ill., April 18, 1934

On this continent, the practice of medicine, while perhaps apparently unchanged, has nevertheless undergone a very marked alteration in its method. Today, organized medical services, of one kind or another, have become established on a very extensive scale so much so, indeed, that much discussion has evolved as to whether or not, in the near future, the new world will emulate those older countries abroad which are now providing, under one name or another, organized medical services.

Sickness is not a personal matter in the sense that its effects are limited to the patient. A communicable disease is spread from the sick to the well. Sickness means loss of income to the patient and decreased production to the community. The vicious circle of disease, poverty and dependence is only too familiar. Obviously, sickness is a national social problem, the cost of which we pay, either directly or indirectly, in every instance.

Glance, if you will, at the vital statistics of this or any other community, and you will find that a large percentage of the deaths which occur may be classified as preventable, and why? This condition of affairs exists because of a universal failure to bring together medical knowledge and medical practice. The most urgent problem in medicine today is not the accumulation of further knowledge, desirable as that undoubtedly is, but to bridge the gap which now exists between knowledge and practice.

This gap is not a new chasm caused by the upheavals of an economic depression. It existed even in our years of prosperity, and it has merely been widened by the depression.

Today, more than ever before, we are concerned with medicine as a service, as one of the social resources of mankind to be used for the benefit of all the human family. In other words, conditions must be so changed as to make the full benefits of curative and preventive medicine available to each and every individual. How is this to be achieved? What are we going to do about it?

A number of explanations may be offered to account for the present undesirable arrangements whereby so many are left without the medical care they need. I believe that the real explanation is to be found in the fact that there is no effort made, under our present system, to overcome the economic barrier which now keeps patient and doctor apart.

The problems arising out of the costs of medical care are usually presented from the point of view of the public, as consumers. We are told that, because sickness is not evenly distributed over the population, in consequence, the costs of sickness are not evenly distributed. We are reminded that, as sickness is unpredictable as to its time of occurrence, severity and cost, it cannot be budgeted for. Furthermore, it is pointed out that wage-earners, who make up the bulk of the population, have, as a rule, no financial resources beyond their weekly earnings. The situation, too, is further complicated by the fact that sickness is most prevalent in the lower income groups. All told, this creates an impossible situation, with the heaviest burden resting on those who are least able to bear it.

There is, of course, a practitioners' point of view to this question of costs of sickness. If the public are unable to pay, the doctor cannot collect the fees he has earned. The sliding scale of fees is used to adjust the fee, according to the medical attendant's judgment, to the ability of the individual or family to pay. Why should a medical practitioner, on this basis, charge his full fee to a thrifty family who, because of their thrift, are able to pay, and reduce his fee to a careless family who, because they are spend-thrifts, are unable to pay? This rather obviously gives an unfair advantage to the prodigal and penalizes the thrifty.

If the sliding scale is to be effective, the physician must be capable of assessing ability to pay. It is also presumed that each medical practitioner will have an equal share of practice among all economic groups in order to even out his fees. Unfortunately, the larger the practice among the poor, the less time or opportunity is there to build up a clientele of well-to-do patients. In any case, it is an unsound economic system to overcharge one individual to compensate for the loss incurred through others, who pay less than the cost of service.

The situation from the point of view of the medical profession is made difficult too because our present system fails in not making adequate use of the recently-qualified medical practitioner. The result is that the whole of the individual doctor's life earnings must be made in a comparatively few years.

Nor is this all, for it has come to be expected that the medical profession will assume the obligation of the State in providing indigents with one of the necessities of life, medical care. Surely it is unsound and unfair that one group, the medical profession, should be made to assume a burden which should be borne by the whole community.

The medical profession are proud of their record of gratuitous service to those who are in need. The members of the profession, in general, are always willing to give a certain amount of free service. Such free service, however, should be entirely voluntary, as is given whenever a doctor provides care beyond that for which the patient can pay.

The problem which faces the public and the medical profession may be briefly stated to be the provision of adequate medical care for all, with reasonable remuneration for those providing the medical care, by making it possible for all to contribute their share of the cost.

National Health Insurance is suggested as one means whereby this problem may be solved. The principle of health insurance is, in a word, to shift the economic burden from the individual to the group. The insured pay a premium to a fund out of which the costs of medical care are met.

I should like to deal with two special features, because a lack of understanding of these distorts the whole consideration of national health insurance.

First and foremost is the fact that the public desire a high standard of

medical services and, at the same time, approve of a reasonable remuneration to the doctor for that service. The public realize, too, that it is they who would suffer most from any lowering of standards. The medical profession, on their part, are anxious to provide medical service of a high standard, and, in return, are entitled to expect a reasonable remuneration.

Secondly, the public evince no desire to interfere with the professional side of medical practice, they are willing to meet the desire of the profession to retain full control in this matter.

There is no public dissatisfaction with the medical profession, indeed, we find the very reverse. The public show an appreciation of medicine and a desire to profit more fully of what medicine has to offer. Public dissatisfaction is concerned with the system of medical practice whereby the benefits of medicine are not available to all.

If we start with an appreciation of these truths, we can then view the medical aspects of national health insurance without the bitterness and lack of understanding which arise if it is presumed that the public and the medical profession are at loggerheads over such basic principles of any system of organized medical services.

The medical aspects of national health insurance cannot be entirely divorced from other matters, such, for example, as organization, because of the relationship between organization, costs, et cetera, and the medical services that are to be provided.

The members of the medical profession unfortunately are apt to be extremely individualistic in outlook. The individual practitioner frequently builds up a rather quaint conceit, based upon the adulation of his patients, displaying a complacency that is amusing but revealing, and, above all, an irritation that anyone who has not successfully passed through the fires of medical training should dare to voice an opinion on the subject of medical care.

The medical profession, after all, hold a strategic position in national health insurance because they have a monopoly of the knowledge concerning the main field of service which it is the aim of health insurance to provide. But just as physicians in public health have learned that their group is but one of several contributing to public health services, so must the practitioner of curative medicine come to realize that medical practitioners form but one of several groups taking care of the sick.

If it is desirable, and I believe that it is, that the organized medical profession control the professional side of the medical services in national health insurance, it is just as logical that, in matters of business arrangements for national health insurance, the lay power be supreme.

The relationship is comparable to that which exists in our hospitals between the Board of Governors, a lay body, and the Medical Board, a professional body. This relationship, despite certain difficulties, works very well, and there is no better system to suggest unless a dictatorship is preferable.

While I hold no special brief for national health insurance, yet, up to the present time, it would seem to be the one method of spreading the costs of medical care which has already been used extensively on a national basis. A number of countries have tried health insurance, and while they make many criticisms of it, not one has given it up, and most have extended its scope. A fair conclusion is that they have, at all events, found health insurance to be preferable to the conditions which existed previously.

The organized medical profession have the right to expect that they will be consulted by any government considering health insurance or other legislation affecting the provision of medical care.

Obviously, there is nothing to be gained by a government's consulting a medical profession whose members have no suggestion to make and no opinion to offer beyond the expression of a pious hope that all will be well if things are left to take care of themselves.

Medical practitioners are given few opportunities to use their skill in keeping people well. It seems unlikely that any large percentage of the population will, as individuals, pay fees for health supervision. The payment of medical fees will always be more or less irritating, because we prefer to use our money to buy something we really want.

There has been a considerable amount of annoyance shown by the medical profession over the invasion, by public health services, of what the profession have considered to be the field of private practice. It is only fair to note, however, that the encroachments which have been resented have usually been into fields left unoccupied until the way was opened by the public health services.

A fair criticism of national health insurance is that it has not been preventive either in outlook or in practice. Health supervision on an individual basis is certainly more desirable and should be more effective than a health clinic service.

National health insurance should signify more than lip service to the desirability of prevention, it should mean the systematic practice of preventive medicine by the medical profession. The health insurance practitioner would be paid for his preventive work, and the economic barrier raised by direct fees would be removed from the path of the patient who wishes health supervision in his doctor's office.

It is impossible to provide an adequate medical service without a properly organized health department. It would be possible, with national health insurance, to define the two fields of public health and private practice. No gaps between them need exist. There need be no duplication, and most of the sources of irritation as between the public health services and the practitioners of medicine would be removed. The allotment of health supervision and active immunization to the general practitioner is both desirable and practical, provided the service is paid for.

There are some disease problems which may best be dealt with through clinics of the public health services. Tuberculosis, venereal disease and

mental hygiene require the active participation of the public health nurse, working in and from the clinic, to interpret environmental conditions to the physician and to see that his instructions are carried out in the home. Clinics in these fields are rightly regarded as being essential in the programme for prevention and control.

Mass methods are not applicable to medical care. Neither patient, nor disease, nor treatment can be standardized. Medical care, to be effective, must be rendered on an individual basis.

Experience shows that the best type of medical care is built around the general practitioner. The first objective of national health insurance should be to make available, to all, the services of a general practitioner.

A good deal of sentiment surrounds the title, "family doctor." The centralization which has resulted from modern transportation, along with other forces, has brought to an end the social organization into which the family doctor fitted. The old-time family doctor passed when medicine advanced beyond the acquirement of personal skills.

The general practitioner of today is quite capable of dealing with over 80 per cent of illness. The present tendency of supplanting the general practitioner by a group of specialists, called by the family according to the age of the patient or the part which appears to be diseased, is unsound.

It is the general practitioner who deals best with the individual patient, whether it be as health adviser or to prescribe treatment, because his is the all-round approach that is based upon a general knowledge of his patient's physical, mental and social condition. It is this more intimate general knowledge of his patient which allows the general practitioner to be effective in the psycho-therapy which so many patients require.

Specialism has modified medical practice. Partially or wholly, temporarily or permanently, some branch of modern medicine is restricted to the specialist by reason of his more complete knowledge and skill in a limited field.

Unfortunately the public go to specialists direct because they find more and more medical practitioners refusing to do general practice, with the result that the public have come to regard the general practitioner as being of inferior quality. The public have also observed that hospital staffs are largely made up of specialists, and the public have found the specialist not unwilling to receive patients without any reference from a general practitioner.

To emphasize the rightful place of the general practitioner is not to minimize the need for the medical specialist and consultant. It seems reasonable that a general examination should precede special examinations, and that a correlation of the findings of special examinations should be made from a general rather than from a special point of view.

National health insurance should require that specialists be designated and that they receive their cases through the general practitioner who seeks their assistance in problems of diagnosis or treatment, and, in certain cases,

to provide the therapy indicated. The general practitioner, under such circumstances, takes on many of the functions of the old family doctor, including that of advising his patient as to where competent specialist service, of the kind required, can best be secured.

Much sentimental nonsense has been expressed about freedom of choice of physician. Freedom of choice is desirable because it means the confidence of the patient in the doctor of his choice which is such a valuable element in medical treatment. Free choice means competitive practice which, since it tends to maintain standards of service, is, within limitations, most desirable.

Real freedom of choice of medical attendant is exercised today only by that minority of the population who can have what they want because they have the money to pay for it. Geographic location and economic status limit freedom of choice in a fairly drastic manner for the majority of people. The only freedom of choice, alas, which most of the people now exercise is to decide when they are "sick enough to have a doctor."

National health insurance would make freedom of choice of physician much more of a reality, because every qualified medical practitioner should be eligible to practice, and the economic barrier would be removed. I believe that if the individual relationship between doctor and patient is to be preserved under our social organization, the only way open is to remove the economic barrier of medical fees which now keeps patient and doctor apart.

The need for health insurance grows out of the inability of the individual or family to make economic provision for medical care. The insured group should be limited to those with an income below a figure which makes it unlikely that they can, individually, make provision for illness. It is difficult to set an arbitrary amount, but an income of twenty-five hundred dollars for those with dependants, and twelve hundred dollars for those without dependants, might be considered.

Under our present social organization, there is no reason why the medical profession should be treated differently from the other professions when it is a question of dealing with the well-to-do. For that group, the question of fees should be a matter of personal arrangement between the patient and his medical attendant.

However, there is no reason why those of the well-to-do group should not, if they so desire, insure themselves against hospital costs, which are a major factor in the economic problem of medical care for those above the health insurance income level.

Sickness insurance was originally intended to provide a cash benefit in lieu of wages lost on account of illness. Later, medical care was provided, and now we have arrived at the time when it is advocated that the only benefit which health insurance should provide is adequate medical care for the insured. Adequate medical care means a complete service, at home and in hospital, by doctors, dentists, nurses and auxiliary services.

It is unfortunate that illness of the breadwinner usually means a loss of

income at the very time expenses are increased as a result of the illness. Nevertheless, it is believed that whatever cash allowance is to be provided, to compensate for lost wages, should be paid out of unemployment insurance and not out of health insurance.

The cash benefit has been the cause of most of the difficulties associated with health insurance. It brings in the question of certification, it drains the health insurance fund financially, and, all told, makes administration and finance unduly difficult.

The medical profession are desirous of divorcing health insurance from all benefits other than that of medical care. To do so makes the service clear-cut in its purpose. The medical profession are not particularly concerned as to the "insurance carrier" except in that they would be unalterably opposed to allowing any insurance carrier to come between the doctor and his patient as regards the professional side of the doctor's services.

Public and profession would unite in demanding that national health insurance should place in the hands of the organized medical profession responsibility for the control of the professional side of the medical benefit. In no other way can the public be assured of a high standard of medical care, available as required, leaving the medical profession free to maintain such a service and, at the same time, to discipline its own members. The best results are obtained by giving responsibility to those who provide the service. Individualism can be carried to impractical extremes, and in any organized service, there must be some control and provision to take care of the few recalcitrants found in every group. Beyond that, there would be no change from the present mode of practice. The medical practitioner would have his private patients and would care for his insured clientele as private patients, except that, for their care, he would be paid out of the insurance fund.

The medical care of the indigents is a responsibility of the State. All the arguments advanced in favor of freedom of choice of physician, et cetera, as being essential to the provision of adequate medical care, are equally valid as regards the medical care of the indigent.

Obviously, it would be undesirable to build up two systems of organized medical services, the one for the insured, the other for the indigent. A satisfactory way would be for the State to pay the insurance premiums of the indigent, and thus discharge an obligation, long overdue, to provide the indigent with medical care at the expense of the public as a whole, and to remunerate those who provide the care.

The general principle of payment on the basis of service rendered receives universal support. There does not appear to be any reason for a hard and fast rule as to how health insurance practitioners are to be paid. A certain sum of money will be available for the payment of the practitioners, and there is no good reason why the doctors of each area should not, themselves, decide as to which method they desire to use.

In those areas where there is not a sufficient population to support even

one general practitioner, it appears that some definite salary must be paid to the doctor so as to assure the area of a medical service and the practitioner of a certain income

In England, the medical profession have selected payment on a capitation basis, which is the payment of a *per caput* allowance for each insured person

In some countries, small fees are charged for a permit to secure medical care when illness occurs, or part of the cost of medicines is paid for, direct, by the patient. The purpose of all such fees is to discourage abuse of the service. It is, however, a serious matter to impose any fee, no matter how small, because the object is to remove the barrier of fees and not to discourage the insured from consulting his doctor. Better some abuse than the loss to anyone of the benefit of early diagnosis and treatment

In conclusion, let it not be forgotten that it is the public—the great consumers—who, ultimately, are going to decide what they are prepared to pay for. This is not the responsibility of the medical profession, they cannot attempt to force upon the public a service for which the public are unable to pay

Still more important, perhaps, is it to emphasize the fact that it is not the responsibility of the medical profession to furnish a service for which the public are able but unwilling to pay. On the other hand, the medical profession should not deprive the public of medical care for which the public are able and willing to pay through National Health Insurance

EDITORIAL

UNIVERSITIES AND MEDICAL PATENTS

At the recent meeting of the American Medical Association at Cleveland, Dr George Blumer introduced a motion, which was passed by the House of Delegates, requesting that a committee be appointed by the Board of Trustees to make a comprehensive study of the situation as to the control of patents covering products and devices used in the practice of medicine.

One of the finer traditions of the medical profession prescribes that the physician shall make freely available to his colleagues and to the public any new medical knowledge which he may have gained, and shall not attempt to restrict the use of this knowledge for purposes of personal advantage.

However, in the last decennium, there has developed on this continent a practice by which the physician patents a medical product or device and then assigns the patent to the university in which he is working, or to some incorporated body allied to the university and created for the purpose of controlling such patents. The university or the allied incorporated body may then market the patent by licensing one or more firms to manufacture and sell the product. Royalties may be paid to the university by such licensees. These royalties may be used to conduct a laboratory in the university to check the character of the product produced by the licensees, they may also be devoted to further research on the product, they may be allotted to general research purposes, and they may be in part expended in payments made to the discoverer or inventor.

This practice is, of course, not confined to the schools of medicine, indeed it is more common in other research departments, as for example in colleges of engineering. The medical patents, however, constitute a special instance since the patenting of medicinal products by medical men appears to violate the traditions of the medical profession. It is no doubt in part for this reason that the American Medical Association is being requested to study the situation. It is also, however, because there are grave doubts in many minds as to whether the very nature of university research will not be altered if financial advantage is to be sought from the outcome of that research.

The purposes for which universities or allied corporations may take out patents are very varied. They may be roughly classed as follows:

- (a) Patenting to ensure financial profit to the discoverer or inventor
- (b) Patenting to ensure an income to the university in which the discovery or invention was made
- (c) Patenting to protect the public against inferior products
- (d) Patenting to prevent, by dedication of the patent to the public, any monopoly being established by a commercial agency

A study of the statements made by universities shows that one or more

of the above purposes are advocated by those whose policy includes the patenting of medical inventions

Patenting to Ensure Financial Profit to the Discoverer or Inventor It does not appear that any university has set up machinery for the administration of patents for the sole purpose of procuring financial profit for the discoverer of the method, substance or device which has been patented. However, in several universities or their allied corporations, the policy has been adopted of allotting some share of the profits to the inventor and in some instances no distinction is made in this respect between medical and non-medical inventions. It may be fairly said then that such institutions have adopted a policy which contravenes an old medical tradition.

This tradition that personal profit must not be derived from a medical discovery is adhered to, it must be remembered, not only by the faculties of medical schools but by the far larger number of physicians who are in the practice of medicine outside of these schools. This tradition and that of free service to the poor are potent factors in attracting into the profession men who view their life work as of a higher order than a trade. It would be a sad loss to the world if such men were to be replaced by a type that felt that money was a sufficient recompense, and that for money alone without the ennobling idealism of the finer traditions of the profession, they would be willing to perform the menial and often repugnant personal services that are a part of the physician's task. The men who bear the brunt of these daily demands are those who are also called on to devote much of their time to free work. In a few instances their income is large, on the average it is little more than the salaries of medical research men. This great rank and file of the profession who have lived up to their part of the medical tradition, that of free service, have felt pride in their colleagues in the laboratory who have refused to profit personally by their discoveries. A tendency on the part of these latter to shatter this fine tradition will be a deep hurt to every true physician, a loss of something spiritual that helped him over the sordid parts of his work.

Patenting to Ensure an Income to the University in Which the Discovery or Invention Was Made The governing bodies of a number of universities have stood by the medical tradition for individuals and have refused to permit their institution to profit from the sale of medical inventions or discoveries. Others apparently feel that such funds are acceptable provided that they be devoted to scientific research.

It is perhaps best not to discuss the ethical questions raised by an institution of learning financing itself by adding to the cost to the public of medical remedies, or to do more than allude to the possible loss of dignity involved when such an institution, which is tax free because it does not operate for profit, manages to secure itself profits from its laboratories by the device of an allied corporation that manages its patent business.

Attention may be drawn, however, to the inequitable distribution of financial rewards that seems certain to occur under any régime of university patents.

It would for example be manifestly unfair if one university were to derive financial profit from work carried on in another institution, and yet just this situation is bound to arise if one institution, which does not patent, publishes its results freely thus enabling another institution, by adding some minor practical adaptation to this work, to take out a patent upon it. It may be predicted that such injustices between institutions will occur until all have adopted the policy of taking out patents or all have forsworn the practice.

Even if, however, all medical schools and institutions were agreed upon a policy of obtaining patent rights upon products discovered or invented in their laboratories it is highly questionable whether in the case of patents on the biologic products the purposes of true equity of return as between various individuals and various schools would be attained under the provisions of the present patent laws. Patents are granted not for the discovery of general laws but for the invention of a device, a method, or a product whereby the principle may be applied. The devising of such a means of application is often of very minor scientific merit as compared with the discovery and proof of the general principle. Yet, were one school to devote its resources in men and material to research on the principle, which is not patentable, the total financial reward might yet go to another institution which made a hasty application of this newly discovered principle, and obtained a patent covering such application.

Our patent laws moreover allow of basic patents which cover not only what is the known method of applying the device or product but all future discoveries in which the basic principle employed is similar. The possible injustices inherent in such basic patents are well illustrated in the instance of the Steenbock patent cited by the British Medical Research Council. This patent, which is owned by the Wisconsin Alumni Research Foundation, covers the process of producing vitamin D in natural substances by irradiation with ultra-violet light. The process was originally applied by Dr Steenbock to the irradiation of foodstuffs. Later, according to the Medical Research Council, it was discovered in England that the provitamin in these natural substances was ergosterol and that the irradiation of pure ergosterol resulted in a product many thousand times more potent in vitamin D than any previously known. English manufacturers found, however, that the Steenbock patent covered the irradiation of any substance and accordingly to take advantage of an English discovery the English must pay tribute to a corporation allied to the University of Wisconsin.

Those who defend this money making function of universities apparently assume that it will have no deleterious effect upon the character of the scientific work in the universities or upon the prestige of the university in the community. One may be permitted to express grave doubts of the validity of these assumptions.

A scientist who has no plans to earn money for himself or his school by his work usually enjoys discussing his results freely with others. Who doubts but that from such free intercourse valuable new ideas are developed?

How ready will the same man be to suggest to another an idea that has a patentable value which he himself might profit by?

No one doubts but what the prime function of the research departments of a university is to develop science, and not the practical applications of science. There are great laboratories and highly trained men at the command of industry to devote themselves more exclusively to the latter objective. It is apparently assumed, however, that since in the university laboratories the practical applications of science are inevitably studied as a part of more general investigations, the university may profit from these practical results of the work, without affecting the interest of the scientist in the broader aspects of his problems. But one wonders whether the measure of a man's university standing will not be insidiously influenced by considerations of the monetary value of his work. Will it be possible not to recognize his contribution to the university funds by according him more weight in council, a more definite right to advancement, perhaps a larger salary? Will there not be envy and bitterness between departments which have profited through patents by increased facilities, a larger staff, more secretarial help, etc., and those whose subject matter contains nothing patentable? Will not the general direction of research in universities be deflected from the goal of all of the truth for its own sake, to that of the part of the truth that has a possible cash value?

It may prove unwise also to assume that the public esteem of the work of scientists will remain as high when it is known that the scientist or his institution has a financial interest which would be affected by the outcome of his researches. There are no doubt individual scientists whose personal prestige is too great to be influenced even by such circumstances. The majority, however, would find that their statements had been trusted not because it was felt that they more than other men were above personal bias, but only because it had been considered that their university position removed them from any temptation.

It seems very doubtful whether the application of additional income from patents to research possesses advantages to counterbalance the restriction of scientific discussion, the inevitable instances of unjust awards, the increase in the lure of applied science, and the loss of confidence on the part of the public which may be reasonably expected if the policy of procuring funds by patenting medical products is widely adopted by our universities.

Patenting to Protect the Public Against Inferior Products It is often stated that one of the valuable ends served by university patents on medical products is the protection of the public against the premature general distribution of dangerously potent remedies, and against inferior products. It is admittedly to the advantage of the public that certain drugs and biologic substances should receive extensive clinical trial under adequate control in some of the large university hospitals so that their value and dangers may be learned before they are placed on general sale. To obtain the material for such trials it is necessary that large scale production methods be em-

ployed and the cooperation of manufacturing firms may be essential. These in return may rightfully expect an advantage in the way of an exclusive license for a time to market the product. A patent may, therefore, be necessary to make it possible adequately to test a dangerous remedy. There may at times also be an advantage to the public if the manufacture of an unusually complex drug or remedy is restricted by the license method to those firms which agree to submit their products to the check of an assay in the university laboratories. Such measures may occasionally be necessary but they certainly should be looked upon as of a temporary and emergency nature and not as a proper function of the universities. If there is to be systematic testing of the therapeutic and the toxic properties of drugs and other medicinal agents on the market it should certainly be carried out on all important products by some governmental agency with power to forbid the sale of substandard goods. At least, however, where a university administers a patent in order that adequate testing of the product be made possible, and receives in return only the extra funds it has disbursed, its motives are plainly above criticism.

At present, it may be remarked, certain drug firms are extremely anxious to be licensed to market any drug or foodstuff the patent of which is owned by a university, and they are especially aware of the advantage of being able to state that each lot is assayed in the laboratory of the university. To obtain the advantages of these good advertising points they are quite willing to furnish in royalties the necessary funds for establishing the laboratory in the university and for subsidizing further research which, they must naturally hope, will still further prove the value of the product in question.

There seems to be ground for criticism in this latter feature—the acceptance of royalties to carry on research on a product already on the market. Ordinary men, even scientifically trained, should not be appointed to work on a problem when the publication of unfavorable results might cut short the source of their own salaries, and when they must constantly feel impelled to hang over the laboratory door the old motto "*Hôm soit qui mal y pense*."

Patenting and Dedicating the Patent to the Public. The criticism is frequently offered that if the medical research worker does not patent his invention it will be patented by some one else who may then establish a monopoly and thus make the public pay far more than they would have had to if the patent had been assigned to a university. If a patentable process or method has been published by one man it can only be patented by another if he modifies it fundamentally. However, since this may occur, a number of scientific men in the past have taken the step of securing patents as a matter of record and then throwing them open gratis to public use. This has not always accomplished all that was hoped for since manufacturing firms have been chary of investing the necessary funds for machinery and for advertising when they had no protection against competition. It is questionable, however, whether any really important medical discovery if patented in this way would be allowed to go undeveloped. Drugs and other

medicinal products possessing important new properties rapidly become self advertising and the demand for them is natural and continuous and does not depend on artificial stimulation. In the case then of important medical discoveries it would seem that the university might well encourage the inventor to patent and dedicate his patent to the public. Since the average medical research worker possesses neither the knowledge, the time, nor the means to obtain a patent, a group of alumni might be formed who would undertake this part of the task, feeling that thereby they were not only gaining friends and acclaim for their medical school but also helping to preserve a cherished medical tradition.

We wish well to the Committee of the American Medical Association. There is a difficult and an important task. The medical schools of the country are sharply divided on the point at issue. It is vital in the interests of equity as well as of good feeling that all should be united again. This can be accomplished, we feel, only by the abandonment of the policy of patenting medical inventions for profit.

The right to patent an invention is not a natural right but a privilege granted by the state to reward inventors. The medical profession as a whole have lived by the rule of relinquishing this reward in favor of the public. It would probably meet with the approval of the medical profession if, following the lead of certain other countries, the United States as a measure of public policy removed from the category of patentable articles all products and devices which are to be used by the medical profession with the purpose of curing or preventing disease.

M C PINCOFFS

REVIEWS

Recent Advances in Sex and Reproductive Physiology By J M ROBSON, M B B Sc (Leeds), F R S E, Beit Memorial Research Fellow, Institute of Animal Genetics University of Edinburgh With introduction by Prof F A E Crew, M D, D Sc, F R S E xv + 249 pages, 14 × 21 cm P Blakiston's Son and Co, Inc, Philadelphia 1934 Price, \$4 00

At the very outset it may be said that the present work is a thoroughly sound and acceptable one in every way, and that it may be unreservedly recommended not only to the laboratory investigator, but also to the increasing number of clinicians who are becoming interested in endocrinological problems. The text is introduced by a foreword from Professor F A E Crew, director of the Institute of Animal Genetics at Edinburgh, whose laboratory has been so productive in the field of reproductive physiology.

The author has arranged his subject matter very logically, and it is surprising how thoroughly he has condensed most of the available worthwhile information into such a comparatively small compass. The secret is obviously in the discriminating omission of discussions dealing with relatively unimportant aspects of the general problem. References to the literature are frequent enough but they are not allowed to mar the readability of the work, as is so often the case. The discussion of the rôles played by the ovarian and pituitary hormones in the cycle, in pregnancy and parturition, and in lactation, as well as the description of the associated cyclical histologic changes, is an excellent epitome of present-day viewpoints. It is perhaps natural that the subject of hormonal control of uterine motility and reactivity, to which the author has made valuable original contributions, has received rather fuller discussion than one might otherwise expect in a work of this size.

There is a short but probably adequate final chapter on Clinical Applications, including a description of the various pregnancy tests. On the whole, however, the chief appeal will probably be to the laboratory investigator wishing to familiarize himself with the present status of research in the field of reproductive physiology, and to the intelligent clinician, particularly the gynecologist and obstetrician, who has the same desire, because of the more intelligent approach to clinical problems which such knowledge makes possible.

E N

Allergy in General Practice By SAMUEL M FEINBERG, M D, F A C P xv + 339 pages, 16 × 24 cm Lea and Febiger, Philadelphia 1934 Price, \$4 50

After reading this book one feels that the author has failed in his avowed purpose of enabling "the average physician to attain a simple direct approach to the handling of this group of ailments," and of showing him "how to care for the allergic patient," not because of any inherent faults in the volume itself but because his purpose is practically impossible of attainment. No branch of medicine is subject to so many variables as is allergy. Basically, one is dealing with a myriad of possible etiological agents, specific in nature, and the clinical effect of exposure to these is again subject to many influences as location, concentration, portal of entry, general health of the patient and many other subsidiary factors. As a result, successful study of these cases presents a problem, except in the simplest instances, that demands the guiding hand of broad experience in finding the significant factors among the multitude of confusing possibilities present in almost every case. No moderate sized book, no matter how well written, can ever hope to do more than present clearly the underlying factors involved in allergy, and this the author has undoubtedly achieved in the present volume.

The material in the book is well organized and is clearly presented. The plan of presentation adheres rather closely to the conventional, beginning with a brief but good historical chapter. There then follows a chapter upon anaphylaxis and allergy which rather satisfactorily explains the relationship between the two. One paragraph in this chapter, in which the author states that all manifestations of allergy are to be considered as being essentially the same, with the same causes, the same method of reaching a specific diagnosis and the same specific treatment, is worthy of emphasis.

His discussion of the importance of asthma in chapter three, in which he mentions the economic loss from asthma itself and calls attention to the disability resulting from its complications, is valuable in view of the laissez-faire attitude of some members of the profession toward this condition. The further consideration of the symptomatology, diagnosis and treatment of asthma follows the usual lines and is well presented.

The section on hay fever is well done and the discussion of hay fever pollens by Durham is especially fine.

The last chapter of the book, devoted to "other allergic disorders," is sound but too brief to be of much practical value in handling these cases.

The case reports are very good and should be most helpful to men just beginning this work.

In conclusion, one might say that, whereas the main purpose of the book is only doubtfully achieved, it can be recommended as giving an excellent brief presentation of the subject.

H M B

That Heart of Yours By S. CALVIN SMITH, M.D., Cardiologist. 212 pages. J. B. Lippincott and Co., Philadelphia. 1934. Price \$2.00.

Dr. Smith has written a number of books on the heart, and in this book he has discussed the heart for the laity. In 10 chapters he describes the normal heart and its troubles. He states "Although the conquest of heart trouble has been made by Modern Medicine, the conquest of troubled hearts rests largely with the individual."

He emphasizes the importance of the mind in considering heart trouble, and in his first chapter he points out the fact that many heart conditions that give the patient apprehension are primarily emotional. "It cannot be stated too emphatically at the outset of this book that heart protests are not heart disease. Better heart health is attained by easing its load, by lightening its burdens, by the proper interweaving of rest and exercise and by correct daily living."

In his next two chapters he discusses the hazards that the heart usually meets in childhood and adolescence and he emphasizes the fact that "the heart is subjected to unusual demands by the changing physiology of a growing body," and emphasizes the place that diseased tonsils play in heart infection.

In his next chapter he stresses the need for heart hygiene in middle life, and in the next two chapters he discusses "signs that may indicate beginning heart trouble and the use and abuse of heart rest," and concludes "When the heart is acutely ill, rest is paramount. As the heart recovers, exercise must be gradually introduced and increased as convalescence advances, if that heart is ever again to become strong and efficient."

In the next two chapters he discusses general suggestions for heart care and in special heart conditions emphasizes the need for temperance in everything, and states "Act your age."

Throughout this book the author has maintained a very sane position and says nothing that would create fear in the mind of the patient.

In his last chapter on "The Psychology of Reconstruction," he wisely states "Stop feeling sorry for yourself."

The physician could well add this book to his library to be used as psychotherapy in those all too common cases that continually come to his attention

J L McC

Modern Drug Encyclopedia and Therapeutic Guide By JACOB GUFMAN, M D, Phar D, F A C P, Consulting Physician, Manhattan General Hospital, New York, formerly Professor of Materia Medica, College of Dentistry, University of the State of New Jersey vi + 1393 pages, 17 X 24 cm Paul B Hoeber, Inc, New York City 1934 Price \$7 50

This encyclopedic compilation of information on drugs is designed to meet the demand of the physician for information concerning the most recent therapeutic agents placed at his command by the laboratories of medical and pharmaceutical research. The volume contains 8,160 modern, non-pharmacopoeial medicinal preparations, comprising 1,878 drugs and chemicals, 535 biologicals, 860 endocrines, 1,563 ampule medicaments, 209 medical foods, 129 mineral waters, 2,344 individual and group allergens and 642 miscellaneous products.

The arrangement of the individual drugs under the various subdivisions of the book is alphabetical. A monograph very similar to that used by the United States Pharmacopoeia or New and Nonofficial Remedies has been employed. Information regarding the physical and chemical properties and therapeutic merit is included. Dosage and method of administration form a special feature of each monograph. Besides the name and location of the manufacturer, information is given regarding the sizes in which the product is marketed.

In addition to the pharmaceutical arrangement and descriptive monographs mentioned in the foregoing paragraph, the book contains a therapeutic guide. In this, the drugs and preparations are arranged under headings which indicate their use in general therapeutics.

Many of the substances which have been the subject of research investigation or controversial medical opinion and discussion in medical literature have appended to them an adequate bibliography.

For convenience and rapidity in finding articles a commercial index has been included. In this, manufacturers are listed and under each heading a list of their specialties and products has been compiled.

In the opinion of the reviewer the volume shows evidence of thoroughness and extensive work on the part of the author. In this day of the passing of the nationally known dispensaries and with the prodigious list of new drugs placed on the market each year by enterprising manufacturers, there is definite need for a volume of this kind.

J C K, Jr

A Text Book of Pharmacology and Therapeutics By ARTHUR R CUSHNY, M D, LL D, F R S, 10th Edition Revised by C W EDMUNDS, A B, M D, and J A GUNN, M A, M D, D Sc 786 pages, 16 X 24 cm Lea and Febiger, Philadelphia 1934 Price, \$6 50

This tenth edition of Cushny's classical textbook appears both substantial in physical make-up, and enlarged in the quantity of subject matter. In the present edition changes have been made to conform with the British Pharmacopoeia of 1932. The authors point out also the inclusion of the newer knowledge on liver and stomach preparations in the treatment of primary anemia, the vitamins, iron medication, bismuth in the treatment of syphilis, new hypnotic agents and the recent advances in

the chemistry of digitalis. In this edition the section on the therapeutic uses of the individually considered drugs immediately follows the discussion of their pharmacological action. Another innovation is the inclusion of a short biographical note of the author in place of the usual preface to the first edition, to point out to the future generations that the "Man was greater than the Book."

The authors retain the general method of presentation, i.e. (1) drugs that are not absorbed, (2) drugs that act after absorption. In the opinion of the reviewer, the book might more effectively accomplish its purpose if the drugs were discussed under the heading of the physiological systems upon which they act. It is stimulating to see the newer theories of the action of drugs on cells mentioned in the text. Perhaps the widespread recognition of these theories will tend to bring about a more quantitative concept of drug action. The manner in which the section on narcosis has been brought abreast of the times is worthy of special mention. It is noted that the theory of Bancroft on narcotic action was not included.

Among some of the newer drugs that have been omitted from the text are dinitrophenol, divinyl oxide, trichlorethylene and tribromethanol. In the discussion of insulin it is observed that the work of Biasotti and Houssay on hypophysectomized-depancreatized animals is not included. It is to be regretted that in many instances the chemical formulae included show evidence of lack of careful revision.

In general it may be predicted that the text will continue to occupy the same important place in pharmacology and therapeutics that it has held for the past 35 years.

J. C. K., Jr.

External Diseases of the Eye. By DONALD T. ATKINSON. 704 pages, 479 illustrations. Lea and Febiger, Philadelphia. 1934. Price, \$7.50.

This book of 15 chapters is a welcome addition to the limited number of works which are devoted exclusively to external diseases of the eye. The following list covers the chapter headings of this work.

Chapter I. A Retrospect of Ophthalmology Relating to External Eye Diseases.
Chapter II. Diseases of the Eye-Lids. Chapter III. Affections of the Lacrimal Apparatus. Chapter IV. Diseases of the Orbit. Chapter V. Diseases of the Conjunctiva. Chapter VI. Diseases of the Cornea. Chapter VII. Diseases of the Sclera. Chapter VIII. Diseases of the Iris. Chapter IX. Diseases of the Ciliary Body. Chapter X. Glaucoma. Chapter XI. Diseases of the Crystalline Lens. Chapter XII. Diseases of the External Muscles of the Eye. Chapter XIII. Hygiene of the Eyes. Chapter XIV. History Taking and Case Records. Chapter XV. Remedies Used in Treatment of External Diseases of the Eye.

While the author states in his preface that the work is limited to those diseases in which a tentative diagnosis can be made without the ophthalmoscope, it is rather difficult to conceive of diseases of the ciliary body, glaucoma and cataract, as external diseases of the eye. In the chapter on diseases of the eye-lids the author has included material which covers not only those conditions seen in this country, but those seen in some of the tropical countries as well.

The illustrations are reproduced both from clinical cases and also from wax models, and as a rule are most excellent, although a few such as pemphigus of the lids require considerable imagination to be able to recognize anything resembling this condition. In a work containing so many illustrations where the visual appearance is the leading point in diagnosis, it is regrettable that stereopticon pictures were not used so that the reader could get, not only a surface appearance, but also depth values as well. Upon the whole, however, the book is to be recommended for both the specialist and the general practitioner.

C. A. C.

COLLEGE NEWS NOTES

Acknowledgment is made of the following gifts to the College Library of publications by members

Dr M B Marcellus (Fellow), Palo Alto, Calif —1 reprint,
Dr W R Riley (Fellow), Battle Creek, Mich —3 reprints,
Dr Hyman I Goldstem (Associate), Camden, N J —1 reprint,
Dr Cullen Ward Irish (Associate), Los Angeles, Calif —1 reprint

Dr Jonathan C Meakins (Fellow and President), Montreal, Canada, was elected President-Elect of the Canadian Medical Association at its annual meeting in Calgary, Alta, June 18 to 22

At the Cleveland Session of the American Medical Association, the Section on Gastro-Enterology and Proctology elected the following Fellows to office

Dr Ernest H Gaither, Baltimore, Md —*Vice-Chairman*
Dr Henry L Bockus, Philadelphia, Pa —*Secretary*
Dr Albert F R Andresen, Brooklyn, N Y —*Member, Executive Committee*

The American Board of Gastro-Enterology, recently organized at Cleveland, elected the following officers

Dr Albert F R Andresen (Fellow), Brooklyn, N Y —*President*
Dr Franklin W White (Fellow), Boston, Mass —*Vice-President*
Dr Ernest H Gaither (Fellow), Baltimore, Md —*Secretary*
Dr Frank Smithies (Master), Chicago, Ill —*Treasurer*

The following were elected additional members of the Board of Regents

Dr George W Eusterman (Fellow), Rochester, Minn
Dr Henry L Bockus (Fellow), Philadelphia, Pa
Dr Sidney K Simon (Fellow), New Orleans, La
Dr Adolph Sachs (Fellow), Omaha, Nebr

At a meeting of the Board of Directors of the Jewish Hospital, Philadelphia, on June 11, Dr Mitchell Bernstein (Fellow) was elected Senior Attending Physician, beginning July 1

Dr Bernstein was elected President on June 5 of the Alumni Association of the Philadelphia College of Pharmacy and Science, from which institution he graduated in 1909, and where he is a member of the Board of Trustees

Dr John Favill (Fellow), Chicago, Ill, has been promoted to the rank of Clinical Professor of Neurology at the Rush Medical College of the University of Chicago

Dr James E Paullin (Fellow), Atlanta, Ga, was made President-Elect of the Medical Association of Georgia at its last annual meeting at Augusta, May 11

Dr Allen H Bunce (Fellow), Atlanta, Ga, was reelected Secretary

Dr Julius H Hess (Fellow) Chicago, Ill, was elected President of the Chicago Medical Society at its last annual meeting, June 19

A public reception was tendered by the Des Moines Chamber of Commerce to Dr Walter L Bierring (Fellow), on June 22, in recognition of his induction into the Presidency of the American Medical Association

Dr William H Robey (Fellow), Boston, Mass, was reelected President of the Massachusetts Medical Society, June 5, at its annual meeting in Worcester

OBITUARIES

JAMES EDWIN HOUGHTON, LIEUTENANT COMMANDER, MEDICAL CORPS, UNITED STATES NAVY

James Edwin Houghton, Lieutenant Commander, Medical Corps, United States Navy, died suddenly at Washington, D C, on May 3, 1934

Dr Houghton was born at Northumberland, Pennsylvania, August 11, 1891 He graduated in 1917 from the Medical School of George Washington University, Washington, D C, and at once entered the Medical Corps of the Navy During the war he served with a laboratory unit Subsequently his service was at sea and in San Domingo and on the Asiatic Station, as well as shore duty in the United States While serving at the U S Naval Hospital at Philadelphia, he was lecturer on tropical medicine at Jefferson Medical College At the time of his death he was Director of Laboratories at the U S Naval Medical School, Washington, D C, and Professor of Tropical Medicine there He had been tentatively selected as the representative from the Medical Corps of the Navy to serve at the Gorgas Memorial Institute of Tropical and Preventive Medicine in Panama He was one of the outstanding bacteriologists of the Navy, as well as a leading expert in tropical medicine He had published a number of professional papers, and had done important work on infectious mononucleosis He had done much work on the technic of the Kahn test and was instrumental in having it adopted as the commonly used test of the Navy Dr Houghton leaves a wife and two children He was made a Fellow of the American College of Physicians in 1926 He was a member of Sigma Chi Fraternity

The loss of so brilliant and promising an officer is deeply deplored by the entire Medical Corps

ADMIRAL PERCEVAL S ROSSITER, M D, F A C P,
Surgeon General, U S Navy

DR JOHN PETER ZOHLN

Dr John P Zohlen, aged 48, a resident of Sheboygan, Wisconsin, died on June 2, 1934, of agranulocytosis, after an illness of four days

Dr Zohlen was born in Germany on September 5, 1886 In his pre-medical training he took his degrees, Bachelor of Arts and Master of Arts, at St Lawrence College, Mt Calvary, graduating in 1909 He attended St Louis University School of Medicine for two years Then he transferred to Marquette University Medical School from which he graduated in 1913 He served an internship at the Milwaukee County Hospital, and became a member of the American College of Physicians in 1930 His specialty was gastro-enterology

At the time of his death he was President of the Sheboygan County Medical Society, and of the Sheboygan Clinic

OTTO A FIEDLER, M D , F A C P ,
Sheboygan, Wis

DR MORRIS HIRSCH KAHN

Dr Morris Hirsch Kahn (Fellow), Fieldston, New York, N Y, died, July 13, at Mount Sinai Hospital, aged 45 years. Dr Kahn, a heart specialist, retired from practice about three years ago because of a heart ailment. He was born at Shklov, Russia, in 1889, came to the United States in his boyhood and attended Cornell University Medical School from which he graduated in 1909. He received the degree of Master of Arts from his alma mater in 1922. He interned at Mount Sinai Hospital, and had been connected with this institution for many years, successively as house physician, resident physician, chief of the clinic for internal medicine and chief of the cardiac clinic. In 1920, he became cardiologist of the Beth Israel Hospital which appointment he held until the time of his retirement.

Dr Kahn was a member of the New York Academy of Medicine, Society for Experimental Biology and Medicine, New York County Medical Society, Eastern Medical Society, New York State Medical Society and the American Medical Association. He was elected a Fellow of the American College of Physicians on December 30, 1926.

He contributed many scientific articles to leading medical journals, including the ANNALS OF INTERNAL MEDICINE.

ROBERT A COOKE, M D , F A C P ,
Governor for Eastern New York

ANNALS OF INTERNAL MEDICINE

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PULMONARY TUBERCULOSIS AS A PART OF A SYSTEMIC INFECTION (HEMATOGENOUS PULMONARY TUBERCULOSIS) ¹

By JAMES ALEXANDER MILLER, A M., M D., F A C P., *New York, N Y*

INTRODUCTION

It is my belief that among general practitioners of medicine pulmonary tuberculosis is usually regarded as a local disease of the lung, produced by the inhalation of tubercle bacilli, and that their ideas of hematogenous tuberculosis are restricted to that form of the disease which we recognize as general miliary tuberculosis

In the light of modern knowledge these are limited and crude concepts of this disease, which greatly hamper our proper appreciation of many important problems concerning its etiology, pathogenesis, clinical manifestations, prevention and treatment

It is my present purpose to review the evidence demonstrating that pulmonary tuberculosis is very frequently a part of a systemic infection, in the hope that this may help to clarify our ideas of this important subject

One of the important objects to be obtained from such a review would be the appreciation of the relationship between first infection with tuberculosis, which usually occurs in early life, and the serious forms of pulmonary tuberculosis which as a rule occur in adult life. In doing so, we will also have occasion to consider the possible desirability of modifying the classifications of pulmonary tuberculosis now in general use in this country

HISTORICAL REVIEW

When Koch first discovered the tubercle bacillus he believed that phthisis was the direct result of a first infection of the lungs with tubercle bacilli. This continued to be the general concept up to the early part of the present century, and Cornet's ¹ handbook on tuberculosis, published in 1904, which was recognized as authority at that time, expresses this view. But it is significant that in this same year of 1904 von Behring ² announced his famous dictum "Adult phthisis is the last tune of a cradle song." But even before that, Petruschky ³ and Hamburger ⁴ had thought of tuberculosis

* Read at the Chicago meeting of the American College of Physicians, April 17, 1934
From the Tuberculosis Division of Bellevue Hospital

as a chronic smouldering infection, and Hamburger particularly, as a pediatrician, classified his cases into early and late forms of the disease. Following the rediscovery and the appreciation of the significance of the primary complex by Albrecht⁵ and particularly by Ghon⁶ in 1912, Ranke⁷ in 1916 built up a very imposing structure about the three-stage evolution of tuberculosis, based upon the theory of blood stream dissemination modified by his ideas of the various states of allergy. Ranke was the first definitely to clarify the idea of phthisis as a final phase of a systemic tuberculous disease which has become localized in the organs, particularly the lungs. In the meantime Maimorek⁸ had demonstrated that tubercle bacilli reach the blood stream within a few hours after the first infection, and Liebermeister⁹ had proved conclusively that bacillemia frequently occurs in tuberculous patients. In recent years Lowenstein¹⁰ has made extravagant claims of the demonstration of tubercle bacilli in the blood, which have not been corroborated by other workers. But the conservative opinion of Wilson¹¹ that bacillemia occurs in about 5 per cent of all patients, and as a transitory phenomenon perhaps much more frequently, is becoming more and more generally accepted.

It is interesting to note that French clinicians in general have always leaned to the idea of pulmonary tuberculosis as a part of a systemic infection. Landouzy¹² coined the term "typho-bacillose" and arrived at his conclusion as to the tuberculous origin of idiopathic pleural effusions because of this point of view. Bard¹³ and Piéry¹⁴ built up a most admirable classification of pulmonary tuberculosis upon this basis, and the more modern phthisiologists such as Rist,¹⁵ Sergent,¹⁶ Bernard,¹⁷ Bezançon¹⁸ all assume that pulmonary tuberculosis frequently represents the extension of a systemic infection to the lungs.

In England, Wingfield¹⁹ has recently offered some very keen observations in support of the concept of the hematogenous origin and evolution of many cases of phthisis.

It is, however, from Germany that the chief recent additions to our knowledge have come. Beginning with Koch, followed by Orth,²⁰ Roemer²¹ and many other experimenters, the idea that phthisis was due to a reinfection rather than to a primary infection was gradually developed. But while the possibility that this reinfection was endogenous was recognized, under the influence of Aschoff²² there was gradually built up the strongly entrenched theory that pulmonary phthisis is due to a new exogenous infection entirely independent of the first infection. The influence of Aschoff and his associates has been very great, and since his visit to this country his ideas have largely dominated American medical thought concerning the pathogenesis of phthisis.

But in the past 10 or 15 years, pathologists and clinicians alike in Germany have been very definitely swinging around to a critical attitude toward Aschoff's ideas. Redeker²³ Loeschcke,²⁴ Duken,²⁵ Schurmann,²⁶ Pagel,²⁷ Rudel,²⁸ and Neumann²⁹ in Vienna all have been stressing patho-

logical and clinical evidence in favor of the close relationship between the first infection and the phthisis which results so many years later

Thus, the issue is drawn between the advocates of exogenous reinfection as the cause of phthisis and those that believe in the endogenous sources of such reinfection

It should be emphasized, however, that no one doubts that exogenous reinfection occurs and is probably quite frequent. On the other hand, it is becoming more and more the accepted idea that the endogenous sources of reinfection have been improperly relegated to the background and are of very marked, if not indeed of predominant, importance

PATHOGENESIS OF TUBERCULOSIS

Primary Infection The primary infection with tuberculosis occurs usually in the lungs, but occasionally elsewhere in the body, particularly the intestinal tract. The original lesion which is produced is usually slight and most frequently is unaccompanied by symptoms. Sometimes, however, it is quite extensive and accompanied by acute symptoms. Associated with the lung lesion there is invariably an accompanying lesion of the neighboring lymph nodes, which in the case of the lungs are the tracheobronchial group. As a rule, these two conjoined lesions become rather quickly quiescent and tend to become calcified, in which phase they are ordinarily recognized either by the roentgenogram during life or by postmortem examination. These two conjoined primary lesions in the lungs and lymph nodes have received the designation of the primary complex.

After this first infection occurs there is a changed reaction in all of the tissues of the body toward tuberculo-protein, which gives rise to the well known sensitization to tuberculin and which definitely changes and tends to localize the tissue reaction to any secondary tuberculous infection which may occur whether from without, which is termed exogenous reinfection, or by dissemination from the original lesion, which is termed endogenous reinfection.

The course of the primary infection itself is variable. The disease may spread acutely from this first infection and rapidly cause death, particularly in young children. Most commonly, however, the lesions subside and become calcified and give no symptoms.

In a considerable number of cases, after a long period of quiescence these lesions which are caseating and partly calcified may discharge tubercle bacilli into the blood stream in varying amounts and at varying intervals. This discharge of bacilli occurs particularly from the lymph nodes. We know that actual pathological healing of these lymph node lesions is very uncertain, even when they appear perfectly calcified they may contain virulent bacilli which may be discharged into the blood. It is from this source that the various forms of hematogenous tuberculosis occur, including certain forms of pulmonary tuberculosis which will be our chief concern in this paper.

Post-Primary Disseminations The discharges of tubercle bacilli from the original primary lesions may occur early or late, often many years after the first infection. In many cases they do not produce disease, under such circumstances it is termed that this secondary infection does not "take." In numerous other cases, however, lesions are formed, which are termed the lesions of post-primary dissemination.

The fact that all of the tissues of the body have become allergic because of the first infection, tends to produce a local reaction wherever these disseminated bacilli may lodge, which tends to localize these lesions. This allergic reaction is a specific one and belongs to the group of reactions which are included under the general term of immunity reactions, but does not produce immunity in the sense of protection against reinfection.

In addition to this allergic change each individual has his or her own constitutional reaction to the tubercle bacillus. This constitutional reaction may be one of great susceptibility or of marked resistance, with all intermediate stages, it may be inherited, it may be racial, it may be strictly individual, and in every individual it is subject to considerable variations during his lifetime, depending upon various general factors many of which are little understood but some of which are connected with such generally recognized conditions as intercurrent or debilitating disease, unfavorable social environment, imperfect nutrition and the like.

The effect produced therefore by dissemination of tubercle bacilli may vary greatly according to the dosage and the virulence of the bacilli, but particularly according to the resistance of the tissues at the time, as affected by the specific and constitutional factors above described.

In the great majority of cases the number of bacilli discharged into the blood is small, the reactions are slight, and the lesions and symptoms produced from them are unnoticed. If a large number of bacilli is discharged at one time, we have an acute general miliary tuberculosis.

In other cases we have fairly severe lesions, with symptoms depending upon the severity and the localization of the lesions. These bacilli may, of course, reach any organ of the body, but the lungs are almost universally reached by this dissemination, because of the vast capillary network of the lungs which acts as a screen for any foreign matter passing through the blood stream. When we have local tuberculous lesions in organs of the body which are not accessible to outside infection, such as the bones, kidneys, lymph nodes, etc., we have no escape from the conclusion that they occurred from blood stream dissemination. In the case of the lungs, however, we have usually thought of these post-primary lesions as being due to exogenous reinfection from the inhalation of tubercle bacilli. That they are very frequently not so produced, but rather come from the blood stream dissemination, just as do these other extrapulmonary lesions, is a concept which is now generally accepted, and our problem is, to attempt to recognize these lesions as such, because they differ very materially in behavior from those due to exogenous reinfections, and because this origin of pulmonary

tuberculosis from the blood stream very materially affects our thinking concerning the incidence and dangers of reinfection of the lungs from the outside. It also adds great importance and significance to the presence and character of the original lesions from which these disseminations occur.

The Character and Evolution of Hematogenous Lung Lesions As a rule, the number of disseminated tubercle bacilli is small, and lodging as they do in the interstitial tissues of the lungs rather than in the walls of the air passages, the symptoms produced are usually systemic at first rather than local. The dose of infection being small, the lesions consequently are small, are productive rather than exudative in character and in general they tend to run a benign course. Coming as they do from infection through the blood stream, these lesions are apt to be bilateral and may lodge in any portion of the lungs but are particularly prone to persist and develop in the cortical areas of the upper lobes, while they tend to absorb from other parts of the lungs. In the majority of the cases they tend to become fibrotic and calcified and are usually recognized in this form by the roentgenogram when there has been no history of obvious lung disease. As these hematogenous disseminations are apt to occur in crops, we may see the evidence of these successive disseminations in the lungs as lesions of varying size and apparently of varying age. At any time, however, during this process a more acute infection may occur, and even to the point of an acute overwhelming generalized tuberculosis which is particularly apt to occur where the lodgment has been in the walls of the blood or lymph vessels, thus making discharge of large quantities of tubercle bacilli an easy possibility.

As the same blood stream infection may reach any organ of the body, these lung lesions are frequently associated with localized tuberculosis in some other organ, and it may be this extrapulmonary tuberculosis which is first recognized clinically. In the overwhelming majority of such cases, however, this is associated with lung lesions also.

In some cases the hematogenous lesions in the lungs and other organs may develop in a protracted but at the same time progressive manner, less acutely than in the case of acute generalized tuberculosis but at the same time in the course of several months producing a widely disseminated tuberculosis in many organs of the body, resulting in death.

In many more cases, however, the lung lesions with periods of quiescence become intermittently active and tend eventually to involve and to break through into the air passages, especially the smaller bronchi. When this occurs, we have a distinct change in the character and evolution of the disease which then progresses just as though the process had originated in the walls of the bronchi as is the case when the infection is due to the inhalation of bacilli. It is then that pulmonary symptoms such as cough, expectoration, hemoptysis, etc., occur. This form of tuberculosis of the lungs is termed bronchopulmonary phthisis.

Bronchopulmonary Phthisis In a considerable number of cases bronchopulmonary phthisis is undoubtedly in association with exposure and

exogenous reinfection in an individual who has already become allergic because of his primary infection. A conspicuous example of such lesions is the ordinary infraclavicular infiltration with which we are all familiar and which is usually described under the term adult form of pulmonary tuberculosis. Here again the upper lobe localization is characteristic, but they are apt, at first at least, to be unilateral and they are not apt to be associated with extrapulmonary lesions in organs not accessible to the outside. When well developed, however, there is little to distinguish such exogenous bronchopulmonary phthisis from the endogenous form which we have already considered.

When once established, this localized form of tuberculosis called bronchopulmonary phthisis no longer tends to spread by the blood stream. Such dissemination may occasionally occur, but is rare. The usual extension of this form of tuberculosis is by what is termed intracanalicular spread, that is, by the passage of tubercle bacilli through the normal canals of the body to other organs or to other portions of the same organ. In the case of the lungs this is by the bronchi and is termed bronchogenic spread, and is the usual method of progression of phthisis from the apex downward in the same lung or over into the opposite lung. This spread is often accelerated by favoring circumstances such as hemorrhage. It is by this same route that the larynx becomes infected through the expectoration of sputum, and it is also by the same method of intracanalicular spread that secondary intestinal tuberculosis occurs, due to contact with infected sputum.

When the localized organic tuberculosis is in an organ of the genito-urinary tract, such as the kidney, again spread of the infection occurs through the normal canals downward to the bladder, or if it starts in the epididymis, upward through the genito-urinary canal to the bladder and to the kidney.

This tendency of bronchopulmonary phthisis to extend by this method of intracanalicular spread makes possible the formation of very considerable lesions within a short time and rapid spread of the disease, and changes the general course of the disease when one compares it with the much slower and finer dissemination of infection which occurs through the hematogenous route.

In general, in every case of tuberculosis, whether it has developed hematogenously or intracanalicularly, the course of the disease is apt to be intermittent, with periods of exacerbation and remission, which correspond to these recurrent discharges of infection.

The course also varies with the amount of such discharge, with the constitutional resistance and the specific allergy of the tissues, both of which vary in different individuals and in the same individual at different times, and also is influenced by certain accidental factors such as the occurrence of hemorrhage or the discharge of large quantities of tubercle bacilli at one time, either into the blood stream in the case of hematogenous dissemination or into the bronchi in the case of bronchogenic dissemination.

An important fact to recognize is that the clinical manifestations of tuberculosis are practically invariably those of a secondary infection, and that consequently primary infection does not afford a true degree of protection, certainly nothing that we can call a true acquired immunity. It is also important to bear in mind that once there is a primary tuberculous focus in the lymph nodes or in any other organ of the body, the absolute healing of such lesions is a matter of great uncertainty, and that consequently the old dictum, "once tuberculous, always tuberculous," is near to the truth, and inasmuch as these slight lesions from which hematogenous forms of tuberculosis arise are so small and so often give no symptoms, the hazards which attend their existence should be more thoroughly recognized, and if a considerable proportion of disabling or fatal phthisis arises from this source then the measures which may be taken to prevent the occurrence of such active disease from them should be thoroughly understood.

CLINICAL FORMS OF HEMATOGENOUS PULMONARY TUBERCULOSIS

Diagnosis The recognition of the hematogenous origin of acute general miliary tuberculosis and of the disseminated protracted progressive forms of the disease, is easy. At the other end of the scale, after bronchopulmonary phthisis has occurred the decision as to whether this occurred from the hematogenous or the exogenous route is extremely difficult, if not indeed impossible.

In other cases the association of a definite type of pulmonary lesion recognized during life, with an extrapulmonary tuberculosis may lead to the inference that both lesions are from the same hematogenous source.

In certain other cases the occurrence of these localized lung lesions, even though apparently healed as they may appear with the roentgen-ray, associated with recurrent mild systemic disturbances of general health, such as chronic poor nutrition, irregular slight rises of temperature, digestive disturbances, undue malaise and fatigability, may lead to the suspicion of a tuberculous infection mild in degree and possibly hematogenous in source as the cause of such symptoms.

In the lungs, these hematogenous lesions at first not being open to the air passages, may produce no pulmonary symptoms whatever. In other cases the first chest manifestation may be an acute pleural effusion, which is probably very frequently of hematogenous origin. In other cases a small calcified nodule may ulcerate a small vessel, causing a slight hemoptysis. Careful study of the roentgenological evidences of tuberculosis will show that these interstitial lung lesions before bronchopulmonary phthisis has developed have a fairly characteristic appearance. They are usually small and multiple and usually bilateral, with a definite tendency to localization in the upper lobes and to marked calcification. In other cases there are very numerous granular densities throughout the lung fields, closely simulating the appearance of a general miliary tuberculosis, but without

any of the acute systemic symptoms of this disease. Such miliary lesions often come in crops, frequently disappear in a period of a few weeks or months, and may reappear at varying intervals, associated with a varying degree of constitutional disturbance, often very slight.

In still other cases there is a tendency for the infection to travel from the interstitial tissues of the lungs along the lymphatics, giving a strand-like roentgen-ray appearance which has been likened to the meshes of a veil. In other cases the lodgment of the tubercle bacilli may cause rapid caseation, with the formation of small cavities with the characteristic punched-out appearance, very thin walls and surrounded by apparently normal tissue, quite different from the appearance of the ordinary cavity of fibrocaseating phthisis. Such cavities often appear and disappear very rapidly, changing their shape easily, and sometimes may develop into ordinary bronchopulmonary phthisis.

The recognition of these clinical forms of so-called hematogenous pulmonary tuberculosis is largely attained by skilful study of the roentgenogram. Naturally, this leaves such interpretation open to differences of opinion and has led to a very considerable discussion as to the actual scientific basis upon which the diagnosis of these hematogenous forms rests. But, in general, as one comes to study these cases and thinks of them in terms of a lack of local symptoms in the early stages and the frequent association with tuberculous lesions in other parts of the body of undoubtedly hematogenous origin, one gets gradually to recognize a group of pulmonary cases which one believes to be of hematogenous origin.

Moreover, frequently in these cases the roentgen-ray will definitely show the remains of the primary complex both in the lungs and particularly in the tracheobronchial lymph nodes, and in the case of the latter often associated with large densities with more or less calcified deposits, but also showing the possibility of caseating lesions still existent.

Classification. Our review of the pathological and clinical manifestations of tuberculosis will now enable us to consider a question raised earlier, namely, the problem of classification.

We have seen that the ordinary disabling pulmonary tuberculosis is bronchopulmonary phthisis, and everybody realizes that this is due to a reinfection, whether this be exogenous or endogenous, and also everybody realizes that this form of phthisis is much more common in young adult life than it is among children. On the other hand, it appears obvious that there is at least a strong probability that many cases of bronchopulmonary phthisis owe their origin to previous lesions which have been disseminated from the primary infection which occurred in childhood, and that in such cases at least the development of the bronchopulmonary phthisis in adult life should be correlated with the earlier manifestations of the same disease. It is also important to remember that the so-called adult type of phthisis really occurs quite frequently in childhood.

But even more important is it to remember that the childhood type of tuberculosis is recognizable in a very large number of adult individuals who have not as yet at least developed bronchopulmonary phthisis, and that also not infrequently in adults the forms of disseminated tuberculosis which we recognize as more common in children, may occur

The question is therefore raised as to whether it is desirable to bring in the question of age distribution in any system of classification, and whether it would not be more helpful to the understanding of the problems involved if we thought rather of the underlying pathological processes and pathogenetic principles

Considering the problem in this way one would rather come to recognize two general clinical forms of pulmonary tuberculosis (1) The form in which the infection travels by the lymph and blood stream, producing lesions which remain closed in the interstitial structures of various organs of the body. It is recognized that while in this closed form frequently few or no symptoms are exhibited and all that we could recognize is the evidence of old quiescent lesions, on the other hand mild constitutional symptoms do occur in such cases, either because of fresh blood stream disseminations or because of lighting-up of mild activity in preexisting lesions

Now, it is in this form of tuberculosis that the lymph nodes are particularly involved, and that as far as the lungs are concerned there are very few if any focal symptoms, and it is this form which is often associated with lesions in extrapulmonary organs

While this is the usual form of tuberculosis seen in childhood, it must be remembered that the lesions in either a quiescent or an obsolete state persist throughout life and can be recognized, so that careful examination of many adults who have no symptoms will definitely demonstrate the presence of this so-called childhood form of tuberculosis

Bard¹⁷ and Piéry¹⁴ devised a very detailed classification of the pulmonary forms of this type of tuberculosis, and Neumann²⁰ has adopted and amplified this classification for clinical use into a very complex system. While the various forms which these authors describe can be recognized after careful study, their very complexity makes them cumbersome and detracts from the usefulness of such classification.*

I have found it simpler and more practicable to include all of these forms under the general designation of lymphohematogenous tuberculosis, while recognizing the fact that this type of the disease develops many various phases during its evolution

(2) In very strong contrast to this type of tuberculosis we have the bronchopulmonary phthisis. Here, we have serious, often disabling or fatal disease with usually definite pulmonary symptoms and with spread of the disease not by the blood stream but through the canal system of the body, particularly in the case of the lungs through the bronchi. This type

*I have described the main forms included in this classification in a previous communication (Am Rev Tuberc, May, 1934)

of disease, as already stated, may occur in childhood but usually does not develop until young adult life. But inasmuch as we have already seen that the recognizable childhood types persist into adult life, the question which arises is: Is the bronchopulmonary phthisis due to an entirely new infection from the outside, or is it due to a flaring-up of these old long-standing childhood lesions? If, as it seems to be true, it often may be due to such lighting-up of childhood lesions, the disease is therefore a continuous one and should be thought of rather in terms of whether the infection is confined in the closed tissues of the body or whether it has gained access to the external mucous membrane surfaces of the bronchi. It is the latter condition which converts it into a serious, disabling disease.

It is a very important and interesting problem not yet solved as to why such latent tuberculosis does not develop more frequently into open phthisis during childhood, and more important still as to why in some cases in adults it so develops into open phthisis and in so many other cases it does not. The correct solution of this problem would undoubtedly lead to the prevention of many cases of pulmonary phthisis which now occur.

The National Tuberculosis Association classification of pulmonary tuberculosis applies in the main to the various stages of this form of tuberculosis, namely, bronchopulmonary phthisis. What we are designating as lymphohematogenous tuberculosis is classified in the American system as the childhood type of pulmonary tuberculosis.

While the National Association classification has a wide field of usefulness, it has the disadvantage of all fixed systems in that it lacks flexibility and encourages the concept of pulmonary tuberculosis as a static process. As a matter of fact, the evolution of tuberculosis is a moving or dynamic process subject to frequent change. The minimal case of today, for example, may be a III C case tomorrow, following a hemorrhage with widespread bronchogenic dissemination of new lesions and with marked constitutional disturbances.

Without discarding the use of this classification entirely, I have found the less static division of cases into (a) the lymphohematogenous type with closed interstitial lesions and extension through the lymph and blood stream, and (b) the bronchopulmonary phthisis type, with extension through the air passages, most helpful in the understanding of the various phases of this kaleidoscopic disease. I believe that the classification into childhood and adult types may be actually misleading.

Prognosis It is obvious from our discussion of the clinical course of these cases of hematogenous tuberculosis that the prognosis in any individual case will depend upon many factors and would be very variable. The important thing would appear to be to recognize the fact that we are dealing with the form of tuberculosis which while it remains in this closed form is apt to run a benign course, with very few constitutional symptoms which usually respond satisfactorily and promptly to rest treatment.

On the other hand, it is important to realize that many of these cases have no symptoms at all during life, but in some of these apparently well people reactivation of their lesions will occur and disabling phthisis result. Once recognized, therefore, this form of tuberculosis should never be entirely dismissed as a negligible condition.

After these pulmonary lesions have gone over into bronchopulmonary phthisis, which as we have seen they frequently do, the prognosis in such cases presents all of the variations and possible seriousness which is well recognized in this form of the disease. Most frequently it is the determination of whether we are dealing with the closed lymphohematogenous form, or the open bronchopulmonary form, that is important from the standpoint of prognosis and of treatment.

Treatment As long as these hematogenous lung lesions remain localized and in the quiescent stage they may need little or no treatment, but the danger of exacerbation being what it is, their recognition calls for the institution of a program of repeated examination and supervision to provide a protective environment which would prevent them from becoming active disease and which also may have the effect of preventing further disseminations of bacilli from the original focus.

The physician recognizing such cases would not put them in a sanatorium, but would have them report regularly for check-up of the general condition and particularly for repeated roentgenological examination. Every effort should be made to keep the state of nutrition of such a patient good, to avoid over-exertion and stress of every sort.

We are all familiar with the results of such a program for children who have tuberculous tracheobronchial lymph nodes and who respond positively to the tuberculin test. They need more rest than the normal child, they are restricted as to hard exercise, they are given more out-of-door life, special attention is given to their diet and the improvement of their nutrition, with the addition of vitamins, particularly of vitamin D in the form of cod liver oil or some of its derivatives. It is in a similar way that artificial or natural heliotherapy may exert beneficial effects in such cases.

What we now have to recognize is that this type of disease is not confined to children, that the danger of development of hematogenous forms lasts into adult life, that the safeguard and the protection which we well recognize is useful for certain children, is equally important for many adults. If cases of this sort are recognized as possible sources of active tuberculosis, there can be no doubt that many of the advanced forms of the disease, including many cases of progressive bronchopulmonary phthisis, could be prevented.

According to our modern ideas, the treatment of bronchopulmonary phthisis after it occurs, whether from endogenous or exogenous reinfection, is the prevention of bronchogenic spread, particularly after caseation and cavity formation have occurred, and this bronchogenic spread we now know can be most satisfactorily and quickly prevented by bed rest aided by suitable

mechanical means, in which term we include the various types of collapse therapy such as artificial pneumothorax and some of the more radical forms of surgical treatment

In general, this form of mechanical treatment is not applicable to the usual forms of hematogenous pulmonary tuberculosis before they have gone over into the stage of bronchopulmonary phthisis

The slow evolution which occurs in many forms of hematogenous tuberculosis of the lungs suggests that it is in this form of the disease that possibly changes in tissue reaction might be artificially produced by some form of specific therapy. This is not by any means a generally accepted idea, but the fact that even the rather generally discredited tuberculin treatment still does appear in certain types of cases to have beneficial results, and that it is still widely used in such definitely hematogenous forms of the disease as occur in the eye or to a less extent in the lymph nodes, leads one to raise the question whether if we apply our mechanical methods of treatment to bronchopulmonary phthisis and limit our efforts in experimentation with specific therapy to the hematogenous forms, we may not be able to look forward to the future development of more successful specific therapy. Not a few authorities, of whom Neumann is perhaps an outstanding example, are using tuberculin widely, basing its use on just such principles. The idea at least gives us a basis of some hope for the future.

Prevention The prevention of disabling lung tuberculosis is in the main the question of the prevention of bronchopulmonary phthisis. This means the prevention of secondary infections, those from the outside may be guarded against by avoiding close association with active sources of infection, those from the inside may be averted by protective measures tending to keep locked-up the infections that already exist, and tending also to keep the general and specific resistance of the individual such that the bacilli which are disseminated do not produce serious forms of the disease.

That this can be done by the program of supervision and protective environment has already been widely demonstrated in the case of children. The extension of this program to similar cases in adults will certainly prevent the development of many cases of progressive tuberculosis which now occur.

The absolute prevention of tuberculosis would appear to depend upon the prevention of the primary infection. That this is not a utopian idea is evidenced by the fact that an increasing number of adults grow up without tuberculous infection, as instanced by the increasing age incidence at which positive tuberculin reactions appear in various groups of the population. The doctrine that the primary infection really protects in some way from tuberculosis must probably be profoundly modified. That this primary infection changes the reaction of the individual to secondary infection is undoubted, but this changed reaction tends toward a more acute form of the disease, and in that sense the individual may die from the effects of his own immunity. This whole problem of the relative protection and relative

danger which lie in the first infection is one of profound scientific and practical interest, which is not by any means completely solved

SUMMARY

1 The usually recognized clinical form of pulmonary tuberculosis is bronchopulmonary phthisis. This form of the disease is always due to a secondary infection, which may be exogenous, but is very frequently endogenous from the smoldering primary focus or from one of its satellites arising in the form of early or late post-primary hematogenous dissemination.

2 Many other forms of pulmonary tuberculosis recognizable by the roentgenological as well as by the clinical features and course, are due to such hematogenous disseminations. Such processes are usually localized in extent and benign in character, and very frequently the individual with them may go through life with but few symptoms.

3 While many of these processes appear, and may indeed be, for long periods apparently obsolescent, and need then no active treatment, it should yet be remembered that such lesions have potentialities for development, at any time, into serious and fatal forms of the disease. Such cases, therefore, should be regularly examined and the general course of their life regulated and supervised. The development of some sort of specific therapy in the control of this type of lesion is also a possibility of the future.

4 Extrapulmonary tuberculosis—excepting intestinal and laryngeal—is practically always of hematogenous origin, and when recognized should invariably lead to the investigation of the lungs which will very frequently also be found involved in the process.

5 Extension and coalescence of the lesions in pulmonary tuberculosis take place for the most part by intracanalicular spread. Bronchopulmonary phthisis is thus produced, in which mechanical treatment plays its chief rôle. Hematogenous dissemination occurs but infrequently as a complication of manifest bronchopulmonary phthisis. Consequently, such acute forms as miliary tuberculosis are rarely seen in this class of case.

6 The division of pulmonary tuberculosis into two broad types, namely, lymphohematogenous and bronchopulmonary, affords a better conception of the dynamic character of the evolution of the disease than does the rigid adherence to fixed or static systems of classification.

The term childhood type of tuberculosis is misleading for the reason that so often the characteristic evidences of this type persist into adult life when they may develop into more serious forms of the disease.

7 The recognition of the importance of these principles and especially of the rôle of systemic infection, leads us to a better understanding of many forms of tuberculosis, to a more rational method of treatment adapted to each individual case, and to the possibility of preventing many cases from developing from the milder into the more serious forms of the disease.

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THE BLOOD SEDIMENTATION TEST ITS USE AS A ROUTINE, ESPECIALLY IN PULMONARY TUBERCULOSIS¹

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IN 1918 Fåhræus¹ first noted an increase in the sedimentation rate of red cells in citrated blood in pregnant women. At once this was hailed as a new test for pregnancy, but it was soon found to be unreliable in the early months when, of course, its importance was greatest. The test is reliable for pregnancy after the twelfth week if no concurrent infection exists, but by that time its diagnostic value has necessarily been lost. Furthermore, it was soon discovered that acute and chronic infectious processes and malignant new growths had a marked effect upon the sedimentation rate.

TECHNIC EMPLOYED

In this work the technic of Cutler² has been used. In brief it is as follows: "Specially designed sedimentation tubes of 1 c. c. capacity are used, graduated into 50 mm. divisions, with 0 at the 1 c. c. level, each millimeter indicating 0.02 of 1 c. c. One-tenth of 1 c. c. of a 3 per cent sodium citrate solution and 0.9 c. c. of blood, obtained by puncture of a suitable vein, are gently mixed in a 2 c. c. syringe and poured into the sedimentation tube. The position of the sedimenting column of erythrocytes is determined every five minutes for an hour. The observations are recorded on charts that have been designed for the purpose, on which the horizontal lines represent the divisions on the tube and the vertical lines the intervals of time. Graphs are then constructed, which not only show the position of the sedimenting column of erythrocytes at any period of time during the first hour, but also portray the changes in velocity that occur during the process of sedimentation."

Walton³ feels that the sedimentation rate should be corrected to correspond to a standard of 5,000,000 red cells to the cubic millimeter as he finds that the rate is markedly increased in proportion to the degree of anemia present. He cites as an example the rate in a normal individual whose blood was diluted to represent respectively blood containing four, three, two and one million red cells to the cubic millimeter. His table reads as follows:

Normal Individual

| <i>5 Tubes</i> | | <i>Rate in One Hour</i> |
|--------------------|--|-------------------------|
| 5 million R. B. C. | | 1 mm |
| 4 " " | | 6 " |
| 3 " " | | 10.5 " |
| 2 " " | | 20 " |
| 1 " " | | 27.5 " |

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934

This method, from the standpoint of scientific accuracy, is probably the ideal one to use. As a practical clinical procedure, however, it is intricate and time-consuming, while that of Cutler is simple and rapid. Furthermore if, as in all my cases, red counts are made at the same time that the sedimentation rate is estimated, allowance can be made for the various degrees of anemia encountered. The procedure now under consideration is a practical office, bed-side or dispensary test that can be done with a minimum of effort, and in which the human equation does not figure in reading the result.

Again, though the most important methods now are those described by Fåhræus,¹ Linzenmeier,⁴ Gram,⁵ Rourke and Ernestene,⁶ and Cutler,² only Gram, and Rourke and Ernestene (besides Walton³) make any attempt to correct the sedimentation rate for fluctuations in red cell count. This should be fairly good evidence that the majority of workers have found the method here employed clinically satisfactory and trustworthy.

NATURE OF THE REACTION

No definite proof of the cause of increased sedimentation rate has been brought forth, but it is being generally accepted that the phenomenon depends upon the amount of cellular destruction going on in the body. In the ordinary wear and tear of life there is constantly present a process of tissue destruction accompanied by a similar amount of tissue repair. To quote Cutler² "Should the amount of tissue destruction pass beyond the normal, then the stability of the blood is seriously disturbed and the red blood cells settle out quickly from the plasma. Regardless of the disease present, whether it be active pulmonary tuberculosis, malignancy, pelvic inflammatory disease, and acute infections such as typhoid fever, or any disease in which tissue destruction is going on at a greater pace than normal, the rapidity of settling of the red blood cells is in direct proportion to the severity of the disease."

Bortree⁷ says that "Various theories have been propounded to explain the alteration in the rate of sedimentation: changes in electrical potential of the cells, alteration of cell volume or mass, viscosity or chemical variance, etc. Present opinion is that the relative speed of sedimentation of erythrocytes is dependent upon the colloidal chemistry of the blood, and chiefly upon the globulin-fibrinogen ratio. In conditions involving rapid destruction of tissue, there is found in the blood an excess of fibrinogen. In any case where the content of fibrinogen in the blood is above normal, the speed of sedimentation is increased. The greater the increase of fibrinogen content, the more rapid the sedimentation rate, so that the two curves run virtually parallel. However, the sedimentation test is so much simpler than a fibrinogen determination that it is to be preferred in clinical work."

LIMITATIONS OF SEDIMENTATION TEST

The test is absolutely non-specific. It is an index of activity of infection or of malignant growth. It is, however, a valuable and useful prognostic aid and in this connection has been used more particularly in gynecology and in tuberculosis. At times it will act as a "lead," as when a patient is seen with practically negative physical and laboratory examinations but with a high sedimentation rate. One can then be sure that there is some process (other than pregnancy) causing active cellular destruction, and search for the offending cause must be continued. Practically all acute infections are accompanied by an increase in the sedimentation rate, but there is no relationship between the temperature curve and the sedimentation curve, nor is there any relationship between the degree of leukocytosis and the rapidity of sedimentation. (Chart 1)

CHART I

DISEASES GROUPED ACCORDING TO SEDIMENTATION RATES (CUTLER)

With an Abnormal Sedimentation Rate

- 1 Chronic infectious diseases, such as tuberculosis and syphilis
- 2 Acute infectious diseases, such as pneumonia, septicemia, acute endocarditis, the exanthemata and acute bronchitis
- 3 Malignancy
- 4 Localized suppurations, such as pelvic inflammatory disease, suppurative mastoiditis, suppurative sinusitis, empyema of the gall-bladder, bronchiectasis
- 5 Acute intoxication, such as lead and arsenic poisoning
- 6 Certain endocrine disturbances, such as thyroid toxicosis

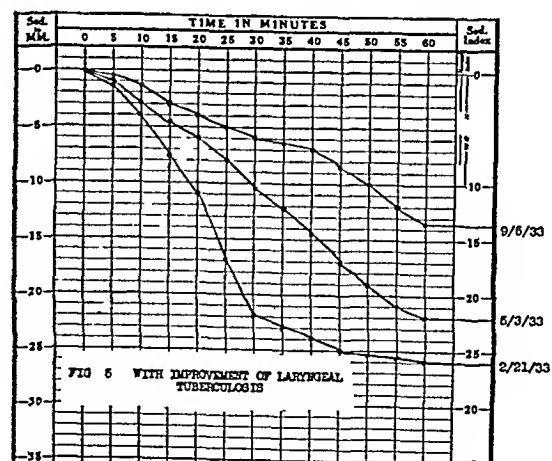
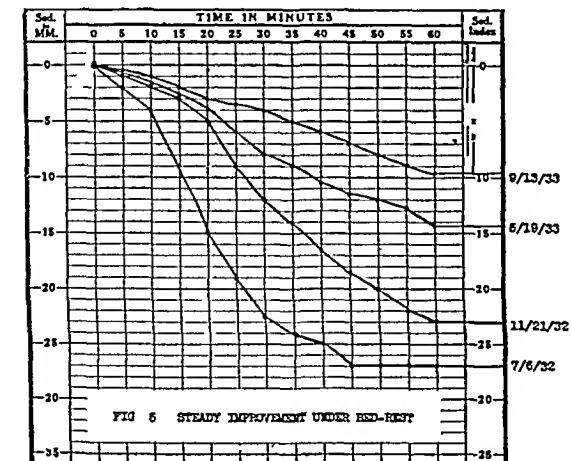
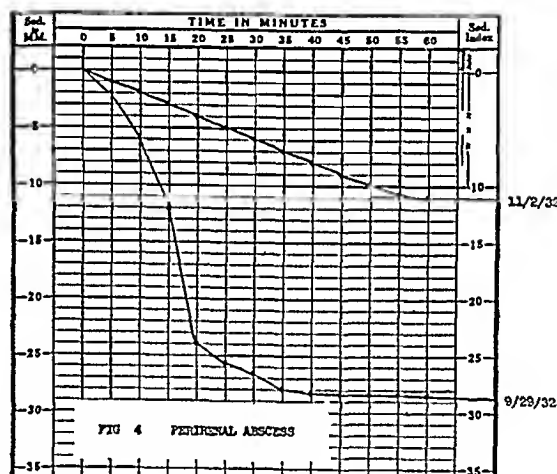
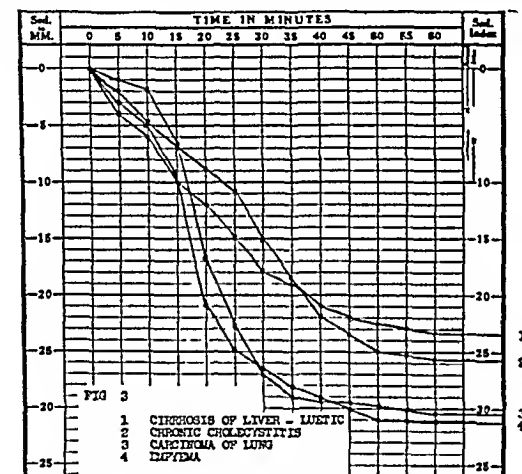
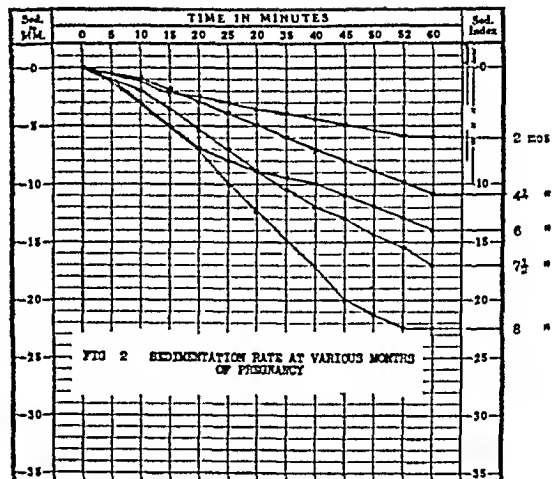
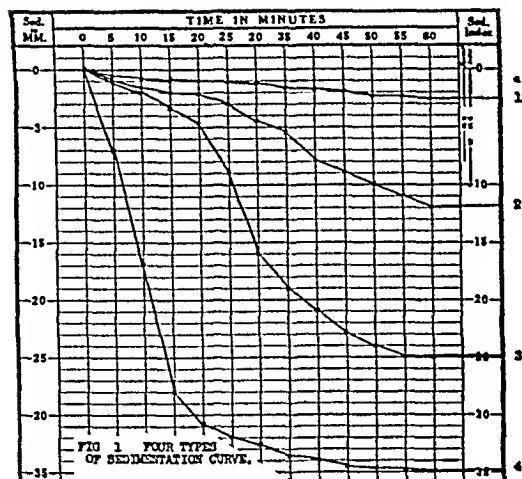
Influencing the Sedimentation Rate Very Little If At All

- 1 Simple catarrhal inflammations, such as acute catarrhal appendicitis, simple rhinitis and colitis
- 2 Chronic ulcerations of small extent, such as gastric or duodenal ulcer

Not Influencing the Sedimentation Rate

- 1 Functional diseases, such as the various neuroses, and neurasthenia
- 2 Certain nervous diseases, such as dementia precox
- 3 Focal infections, such as abscessed teeth, diseased tonsils and chronic sinusitis
- 4 Metabolic diseases, such as uncomplicated diabetes and essential hypertension
- 5 Allergic diseases, such as asthma and hay fever
- 6 Most skin diseases
- 7 Simple growths, such as fibroma, lipoma and fibromyoma
- 8 Simple cysts
- 9 Chronic valvular disease of the heart

It is generally conceded that in tuberculosis the sedimentation test represents the intensity and degree of activity of the process. Walton³ states that "a normal sedimentation rate has never been found with an *active* tuberculous focus." I cannot agree with this statement, but of course the same definition of "activity" must be employed. The one that I prefer is "Activity is present when the patient is suffering from symptoms, which symptoms are due to tuberculosis." Adopting that as a standard, I have seen many individuals with a normal sedimentation rate who had unquestionable evidences of activity.



It is true that in tuberculosis the sedimentation rate is an excellent guide to progress and most closely parallels radiological changes. If the roentgen-ray findings are equivocal, as they so often are, the nature of the sedimentation test will often determine the direction in which the patient is headed. Roche⁸ uses the sedimentation rate as an index for the beginning of exercise and even in the presence of normal pulse and temperature rates waits until the sedimentation rate is approaching normal before allowing exercise. Again, if a patient is simply not "feeling fit" and yet presents no objective symptoms, a normal sedimentation rate would point toward a nervous etiology rather than an organic one. A rise in the sedimentation rate may precede hemoptysis. Repeated tests are very valuable as the rate will change rapidly for better or for worse. From an economic standpoint, the ease and practical costlessness of the test add to its value.

The sedimentation test is not a substitute for any existing clinical or laboratory procedure but is complementary to them. The test is not infallible, but neither are the majority of laboratory procedures. Very rarely, in less than 1 per cent, a normal rate will be found in the presence of active clinical disease, save in certain cases of tuberculosis as mentioned above.

Types of Graphs (Figure 1)

All authorities recognize four distinct types of graph

- 1 A horizontal or practically horizontal line,
- 2 A diagonal line,
- 3 A diagonal curve,
- 4 A vertical curve

The nearer the line is to horizontal the more normal it is, but thousands of observations have fixed the high normal limit at 8 mm in men and 10 mm in women.

Figure 2 shows the nature of the curves at various months of pregnancy. I was able to obtain these through the courtesy of my colleague, Dr R. A. White, of Asheville.

Figure 3 shows the curves in four widely different conditions coming under my observation, namely,

Cirrhosis of liver—luetic
 Chronic cholecystitis
 Carcinoma of lung
 Empyema—non-tuberculous

Figure 4 is that of a patient who had been wrongly diagnosed as a case of acute fibrinous pleurisy. The clinical picture was not that of pleurisy and the high sedimentation rate pointed to something else. In a few days a perirenal abscess was discovered, evacuated surgically, and recovery set in. The sedimentation rate rose shortly to within practically normal limits.

My work on the sedimentation test in tuberculosis is based on 272

patients, in whom a total of 552 sedimentation rates were made by my technician, Miss Mary Roach, 204 of these patients had diagnosticable tuberculosis, of the remaining 68, there were 51 that were diagnosed as having no definite disease, many of these having requested examination because of relationship to or contact with tuberculous patients. The remaining 17 patients had conditions which are not of sufficient importance to be enumerated in detail in this communication, though certain outstanding ones are mentioned.

Of the 204 having tuberculosis, there were 44, or 21 per cent, in stage 1, 54, or 27 per cent, in stage 2, and 106, or 52 per cent, in stage 3, the classification being that adopted by the National Tuberculosis Association and corresponding to minimal, moderately advanced and far advanced, respectively.

Due perhaps to an innate dislike for long and complicated tables, I have felt that it would be most instructive to cite various typical cases showing the reliability of the sedimentation test as a corroborative and occasionally as a warning factor as to the progress of patients suffering from tuberculosis.

Figure 5 shows the sedimentation rates in a man with a far advanced bilateral tuberculosis in whom any type of pulmonary compression was out of the question because of the anatomical distribution of the lesions. Fifteen months of bed-rest brought about quiescence of the pathological process and corresponding slowing in the sedimentation rate.

Figure 6 shows the improvement in the sedimentation rate in a patient with advanced but stationary lung disease, but with a severe laryngeal tuberculosis. Under treatment by the actual cautery at the hands of Dr. J. B. Greene, of Asheville, marked improvement took place in the laryngeal condition which was faithfully reflected in the change in the sedimentation rate.

Figure 7 is from the records of a most remarkable case—a patient with marked bilateral pulmonary involvement who did badly for three months, a pleural effusion developed on the left side (that of major involvement) and immediately marked clinical improvement set in, which is apparent from the slowing in the sedimentation rate.

The next two cases are in what I term the "warning" class. Figure 8 shows the rate in a patient with minimal physical and radiological signs of disease and clinically symptom-free. The roentgen-ray and physical signs remaining stationary for several months, she was allowed to return to her home in Washington classified as "apparently arrested," despite the fact that the sedimentation rate had remained practically stationary. Within one week of her return she had a profuse hemoptysis which was repeated within three weeks, and resort was had to artificial pneumothorax, as a result of which she is now doing satisfactorily. I believe I was guilty of an error of judgment in allowing the girl to discontinue her cure in the absence of a normal sedimentation rate, though I believe she would have had her hemoptysis just as promptly in Asheville as in Washington.

Figure 9 is that of a patient still under treatment, with an advanced lesion of the left lung with cavity formation. Pneumothorax was successfully induced, but adhesions prevented the closure of a four centimeter cavity. Internal pneumolysis was then successfully attempted by Dr Julian Moore and the cavity was reduced to two centimeters in diameter. This patient is in excellent clinical condition, well up in weight, fever-free, coughing and expectorating far less than before her pneumolysis, but the persistently high sedimentation rate is ominous and I fear that she is headed either for a hemorrhage from the as yet unclosed cavity or, more probably, for a spread of disease in the contralateral lung, which unfortunately is not free of involvement. Time alone will tell the tale, but the sedimentation rate in this patient has caused me to handle her most carefully.

The next four cases illustrate improvement noted in patients subjected to various forms of pulmonary compression.

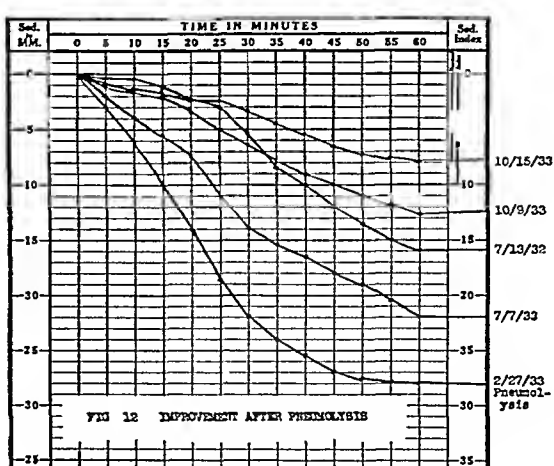
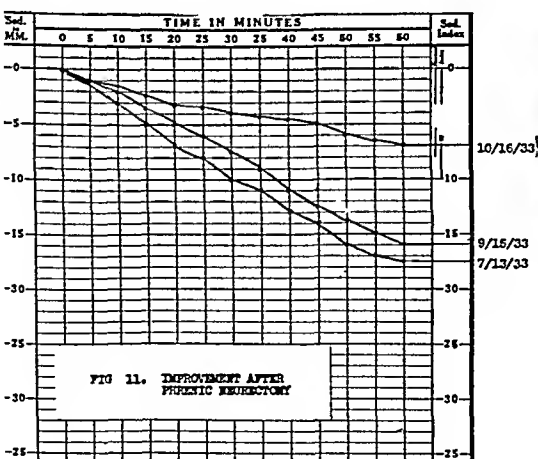
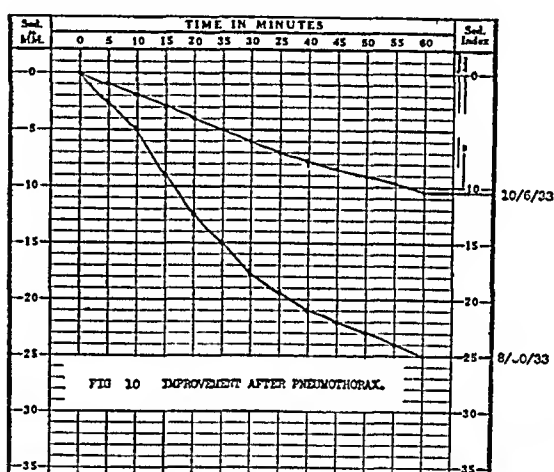
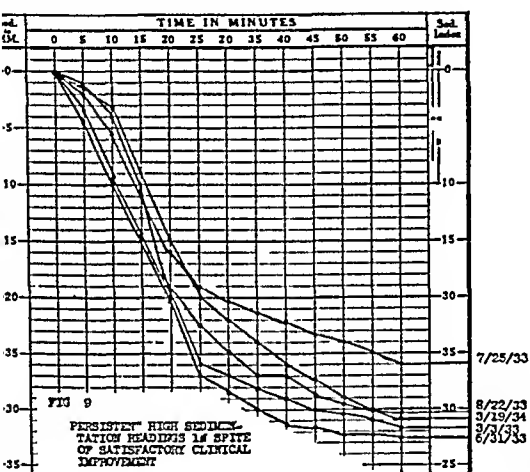
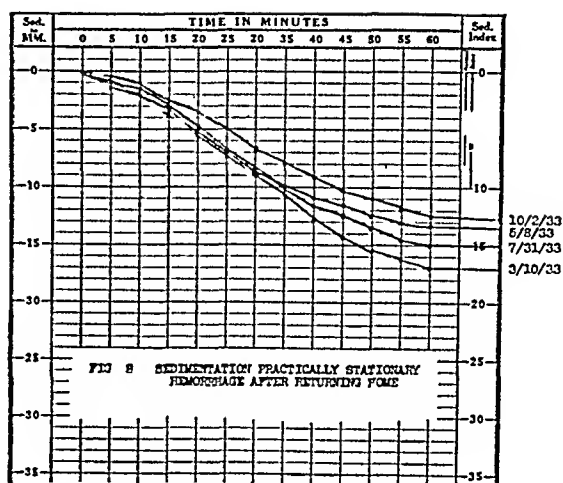
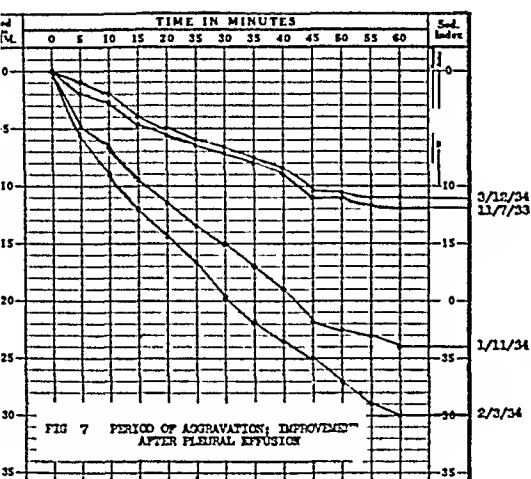
Figure 10 shows the marked slowing in the sedimentation rate after five weeks of treatment by artificial pneumothorax. The patient, a slip of a girl, had a very active, wholly unilateral process. The results following compression were clinically startling: prompt disappearance of fever, practically total suppression of cough and sputum and corresponding physical betterment. The slowing in the sedimentation rate is certainly striking.

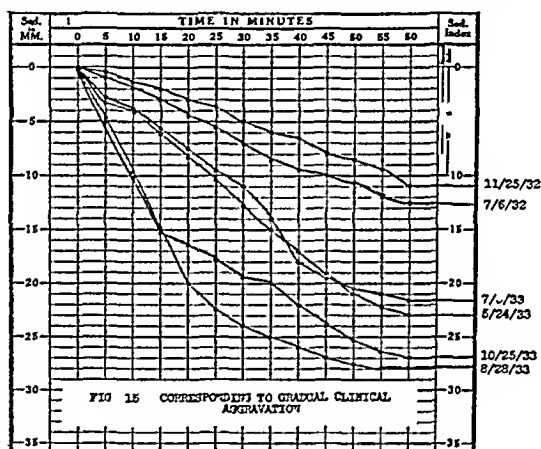
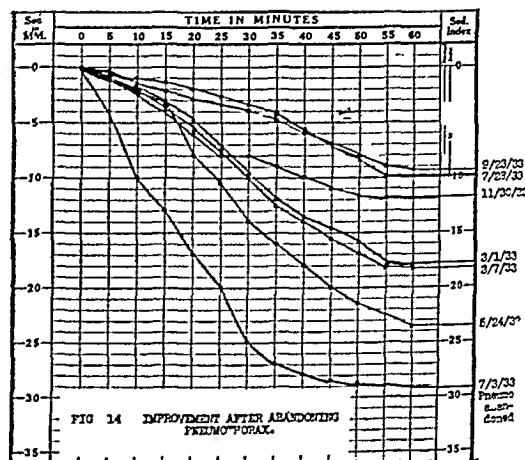
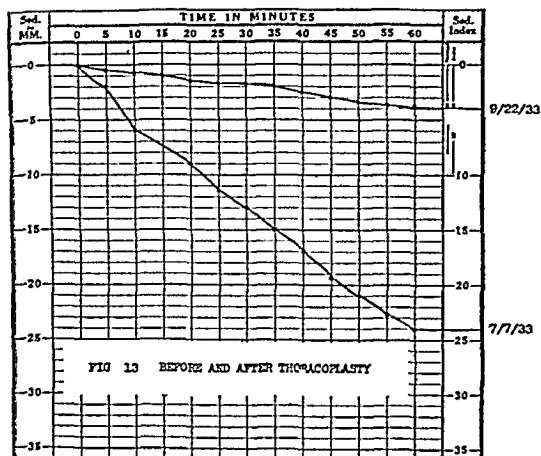
Figure 11 illustrates betterment as evidenced by the sedimentation rate in a patient with an apical cavity in whom artificial pneumothorax could not be induced because of adhesions. A phrenic neurectomy was done by Dr Julian Moore, rendering the patient symptom-free and showing within a month marked slowing in the sedimentation rate.

Figure 12 is from the records of a patient with unilateral cavitation who, after several months of bed-rest with no improvement, was given artificial pneumothorax, but, as so often happens, the cavity was held open by adhesions. An internal pneumolysis was successfully done, again by Dr Moore. Clinical improvement was gradual but steady, as is shown by the four sedimentation rate estimations between February and October, 1933. While the patient still has a pleural effusion, he is clinically well and wholly symptom-free.

Figure 13 shows the rapid improvement in a patient with a far advanced fibro-caseous tuberculosis of one lung. She was definitely on the downgrade when a three-stage paravertebral extrapleural thoracoplasty was begun by Dr W P Herbert about July 15, 1933. Remarkable clinical improvement was brought about, improvement which is borne out by the marked slowing of her sedimentation rate. It must be remembered that within practically four weeks this patient was subjected to three major operations which greatly exhausted her physical resources.

Figure 14 is an interesting one. The patient had a unilateral cavity for which artificial pneumothorax was successfully instituted. Mechanically the procedure was a success. The cavity was closed but the patient did not do well. No spread of disease could be found in the contralateral lung.





Digestion was bad, anorexia ensued, loss of weight resulted and her last state was worse than her first. On July 3, 1933, pneumothorax was abandoned, the air remaining in the pleural cavity aspirated in an effort toward aiding the compressed lung rapidly to reexpand. The patient literally took on a new lease of life. Note the marked change in the sedimentation rate between July 3 and July 28, 1933.

Figure 15 well illustrates the changes in a patient gradually but steadily going downhill over a period of almost 16 months despite the induction of an artificial pneumothorax and the performance of a phrenic neurectomy. This patient has never had enough resistance to go "over the top," a fact which the sedimentation rate emphasizes.

As a result of two years' experience with this test and because of the results obtained as evidenced by the charts shown here, I feel that it is one of real value. I agree with Townsend⁹ that it parallels the severity of the disease. Banyar¹⁰ believes that no tuberculous patient should be discharged until the rate is normal. I am rather in agreement with him, having in mind the girl whose graphs I have shown and who had a hemoptysis within a

week after her return home. From all clinical evidence, this girl should have had a normal sedimentation rate, yet she could never quite obtain one. Walton³ has such an excellent paragraph on the value of the test that so exactly reflects my own conclusions that I cannot refrain from quoting him:

It is a most delicate and sensitive reaction, which reflects very faithfully the state of equilibrium of the blood in relation to any pathological process. It is not specific for any disease, therefore, its uses as a specific diagnostic agent are almost limited to the domain of tuberculosis, where it may be employed in conjunction with a small provocative dose of tuberculin. Used cautiously, however, and as an adjunct to the clinical picture, the sedimentation test, if correctly interpreted, will be found to possess great value, and will often weigh down the scales of differential diagnosis.

In my own experience, based mainly upon cases of pulmonary tuberculosis, I have come to rely greatly upon it, feeling that it reinforces physical, radiological and symptomatic evidence, and frequently presages oncoming evil, or, on the other hand, gives one confidence in the ultimate outcome when clouds loom dark on the clinical horizon.

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THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS *

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AN analysis of our present knowledge of the advances made in the treatment of pulmonary tuberculosis clearly indicates that rest is the foundation and its development the only important and successful remedial furtherance in the treatment of this disease. Detweiler is credited with being the first to advocate rest as a therapeutic measure, but Joseph H. Pratt points out that Trudeau indorsed it before Detweiler. From a surgical standpoint, the development of rest as a curative method forms the basis of modern phthisiotherapy.

Valuable adjuncts to bed rest are postural rest on the diseased hemithorax and shot-bags placed on the front of the chest when the patient lies in the dorsal position. It is true that these expedients prove sufficient to bring about a recovery in many cases of pulmonary tuberculosis in the early, and even in the moderately advanced, stages. However, if cavities have already formed, the rest regimen is too often a failure because of the frequency of bronchogenic extension of disease to the same and opposite lung, the larynx and gastrointestinal tract.

The importance of closing cavities promptly is gradually being recognized, and valuable time is not wasted so grievously on prolonged sanatorium routine while other vital means could be utilized. The ever present possibility of disease extension is not the only danger to be regarded, for there is also the additional menace to the health of others. We have for an illustration the ambulant cavity case who looks and feels well, except for cough and expectoration. It is self-evident that the sooner the cavity is closed the better—not only for the individual patient, but for those who live and work with him.

The ambulant cavity case as a carrier is strikingly shown by our experience with salesgirls employed in a ladies' specialty shop, where one after the other (numbering six) developed tuberculosis. The source of infection was unquestionably traced to the personnel manager, who eventually presented himself for examination, which disclosed bilateral cavity formation. By his own admission, he had been tuberculous for years.

The unsatisfactory results of prolonged bed and postural rest, and the danger of delayed closure of cavities demand the immediate utilization of other methods of hastening recovery in this type of case. If no signs of improvement are seen after a reasonable trial of bed rest, postural rest and shot-bags, other methods of obtaining the needed relaxation for the lung

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should be employed without further procrastination. The proposed operative procedures are those included under the term "collapse therapy," their basis consisting in providing rest for the lung through its collapse. This paper does not allow a full discussion of these methods, many of which are of questionable merit, therefore, my remarks will be confined only to those having widespread acceptance and known to be of established value, with a superior background of experience, namely, artificial pneumothorax, intrapleural pneumolysis, phrenic neurectomy and thoracoplasty. Extrapleural pneumolysis, intercostal neurectomy, scalenotomy and direct cavity drainage are applicable in a few selected cases. This contribution is based upon 25 years' experience with artificial pneumothorax, during which time approximately 1700 cases have been subjected to it, in addition, about 1000 cases have had the benefits of such surgical collapse procedures as intrapleural pneumolysis, phrenic neurectomy and thoracoplasty. Extrapleural pneumolysis and direct cavity drainage were employed in a few cases.

When collapse therapy has been decided upon, the first method to be considered should be artificial pneumothorax, although some surgeons still contend that thoracoplasty is the method of choice. But I do not believe such statements come from those having pneumothorax experience, as, among the latter, the feeling is predominant that every candidate for collapse therapy should be granted a pneumothorax trial.

ARTIFICIAL PNEUMOTHORAX

Artificial pneumothorax is the simplest and most efficient method of putting the lung at rest by collapse. One great disadvantage, however, is the necessity of protracted continuation of the collapse, whereby the treatment often becomes a tiresome affair for the patient, yet, if all goes well, the patient ultimately has a good functioning lung instead of a permanently collapsed one,—as will be the case if major surgical procedures are adopted.

The danger of complications in pneumothorax is negligible, less than 2 per cent of our series died as a result of complications. Since using carbon dioxide for primary inflations, we have not had a gas embolism in 10 years.

Artificial pneumothorax should be used much earlier than is generally the custom. It is indicated in pulmonary tuberculosis with beginning infiltration and a positive sputum, as well as in moderately advanced cases. If no amelioration is forthcoming from a three to five months' routine of strict sanatorium care, and if clinical and roentgenologic study reveals a progression of disease, or at least the response to treatment has been unsatisfactory, a pneumothorax should be attempted at once. A good general rule is to induce a pneumothorax on every cavity case, unless there is some contraindication. When it is known which lung is the source of bleeding, hemoptysis is an obligatory indication for pneumothorax. Tuberculous pleurisy with effusion should be aspirated and continued as a controlled pneumothorax. This is also the best procedure to follow with tuberculous

spontaneous pneumothorax. Exudative types of tuberculosis are no contraindication—good results will be obtained, provided a satisfactory collapse is established, notwithstanding arguments that the consolidated lung cannot be collapsed. This is admitted, but if the patient survives the softening phase, the lung will at least be separated from the chest wall and active collapse can follow as excavation takes place. We have seen this successful time after time.

The contraindications include renal or cardiac failure and extensive emphysema. Tuberculosis of the larynx and intestines, unless uncontrolled and causing a significant hindrance in the patient's nutrition, is no contraindication, neither is controlled diabetes a contraindication.

My associates and I have often called attention to the constituents upon which successful pneumothorax therapy depends, but they may be repeated here. According to our experience, determining factors are (first) the type of disease, its character, degree of activity, complications and condition of the opposite lung, (second) the character of the pneumothorax, (third) social and environmental conditions influencing the length of treatment. If the latter issue is satisfactory, the results of treatment will depend (first) on the type of disease, (second) on the character of the pneumothorax, (third) on the condition of the opposite lung. Admittedly, cases with the disease confined to one side are preferable. But the presence of even active disease in the contralateral lung is not a contraindication per se. We have repeatedly witnessed the healing of a contralateral lung lesion following establishment of a satisfactory pneumothorax on the homolateral side. Cases with a more or less stationary cavity on one side, with progressive bronchogenic extension to the opposite lung, can best be treated by establishing a pneumothorax on the side of the fresh invasion. As collapse on the newly invaded side progresses, and if the mediastinum is mobile, it will shift and fibrosis will proceed on the cavity side. We have had numerous successes by following this technic. There should be no hesitancy in closing cavities as soon as possible by progressive collapse or compression, instead of relying upon partial or selective collapse in this type of case.

In fully 20 per cent of cases selected for pneumothorax, dense pleuritic adhesions will prevent any gas introduction, these require other surgical intervention (noted later), unless contraindications are present. Several years ago we analyzed a group of cases of the above type, wherein a pneumothorax was indicated but adhesions prevented any gas introduction. These cases were subjected to extended sanatorium care, with the result that less than 7 per cent recovered. Had the advantages of modern surgery been attainable, I am certain that fully 40 to 50 per cent would be alive and well.

In a second group of cases studied, pleuritic adhesions prevented sufficient functional rest and closure of cavities in approximately 40 per cent. While gas was introduced and a partial pneumothorax established, recovery followed in no more than 15 per cent. Thus, in 60 per cent of cases selected

for pneumothorax, it either cannot be used, or satisfactory collapse cannot be obtained. This latter class of case is perhaps subject to more debate as to the program to be followed than any other.

We have frequently seen unfortunate instances wherein an unsatisfactory collapse was continued for a lengthy period when it could be clearly shown that pleuritic adhesions inhibited closure of a cavity, undoubtedly, a small number of such cases will recover, but eventually in the majority, extension of disease into the opposite lung becomes manifest, or, if already present, such critical incursions will have been made that the patient's state is hopeless. It is painful to realize that the disease process is allowed to advance in so many cases when the advantages of surgery, if used earlier, would be so beneficial.

In a third group of cases subjected to pneumothorax the collapse was a satisfactory one—often in spite of adhesions—and approximately 50 per cent recovered. If one could persuade the patient to continue the pneumothorax for an appropriate length of time, and to give proper cooperation in taking the cure, the number of recoveries would be decidedly increased. That pneumothorax should be withheld until after a probation of sanatorium care is not in keeping with the advances made in the treatment of this disease by collapse therapy. Too many sanatoria do not utilize collapse therapy beyond artificial pneumothorax, and their first gesture toward surgery is confined to phrenic neurectomy. Beyond that, many institutions are unprepared to carry out the necessary collapse therapy program.

This brings me to a consideration of the surgical treatment of adhesions,—that is, the conversion of an unsatisfactory pneumothorax, because of adhesions, into a satisfactory one. We have never regarded the open operation appropriate for severing adhesions, but for years we did advocate active stretching of adhesions by gradually increasing the intrathoracic pressure—with end results that were far from satisfactory. In 1925, we adopted the closed intrapleural pneumolysis proposed by Jacobaeus, and I later modified it by substituting the high-frequency current for cutting purposes in place of the galvanocautery, which was defective because of the patient's reaction to operation, the character of cutting, and the too frequent incidence of complications.

As already stated, an uncollapsed cavity is a menace to the patient and others in close contact. If efforts to close tuberculous cavities by artificial pneumothorax have been defeated by adhesions, and the patient still raises a positive sputum after three to five months, one should consider surgical attack upon the retarding adhesions at once.

INTRAPLEURAL PNEUMOLYSIS

There is need of a better understanding on the part of those who ignore this most neglected of collapse therapy procedures. A tuberculosis specialist with no surgical training hesitates at attempting the operation—and rightly

so—for, while it is not difficult, some surgical training is necessary to prevent and combat complications which might arise. The surgeon undertakes it reluctantly because he lacks a pneumothorax experience, and often has no knowledge of thoracoscopy. Unaccustomed to operating under the guidance of the thoracoscope, and believing he can more accurately visualize the operative field, he prefers the open method of severing adhesions.

The open operation, however, is unnecessary, because one can place the thoracoscope in such a position as to afford examination of every part of the pneumothorax cavity, which is impossible with the unaided eye. After experience, one can recognize the structure of tissues much better with the thoracoscope and confidently sever large adhesions that could not be cut by the open operation without great risk to the patient.

The dangers of hemorrhage, bronchopleural fistula and empyema are slight when proper technic is employed. While we have given up the galvanocautery of Jacobaeus in favor of my electrosurgical method, we do not condemn the cautery as dangerous—we simply believe the electrosurgical method, while perhaps technically more difficult, is the method of choice because the undesirable aspects of the galvanocautery are excluded.

The operative technic has been fully discussed previously^{1,2,3,4}. For those uninformed about the operation, I will briefly state that in the closed intrapleural pneumolysis, instead of making the opening through the chest wall, after the resection of ribs, sufficiently large to permit surgical ligation and cutting of adhesions—which, after all, is a major operation for the patient—a site is selected for introducing the thoracoscope and after local anesthesia infiltration of that area, the optical instrument (thoracoscope) is introduced by means of a trocar and cannula. A study is then made of the pneumothorax cavity and a site selected for similarly introducing the cutting instrument under local anesthesia through a chest wall puncture. For additional enlightenment, I would refer to my publications.

Technically, as far as the patient is concerned, the operation is a very minor one, scarcely less objectionable than a pneumothorax refill or diagnostic puncture. Adhesions will be present in almost half of the cases selected for pneumothorax treatment, but they will not necessarily prevent a satisfactory collapse or compression of the lung, hence, the mere presence of adhesions is no indication for operation.

Intrapleural pneumolysis is indicated where roentgenologic and clinical evidence discloses (after three to five months' trial) that adhesions are retarding a satisfactory collapse of the lung, provided one can assume that recovery will take place after a satisfactory pneumothorax has been established. Furthermore, adhesions must be of an operable type, and the pneumothorax sufficiently large to permit manipulation of instruments. The operation is also indicated when uncomfortable symptoms from downward pressure on the stomach and liver are apparent (even in satisfactory pneumothorax) in endeavors to maintain a proper collapse by high intrathoracic pressure. A still further indication is one wherein adhesions have

become fibrous and are causing an early expansion of the lung by their contraction,—thus often inciting hemorrhage or recurrence of tubercle bacilli in the sputum

Complications In over 250 cases operated upon we have had no direct operative mortality. In our series only one death occurred for which the operation was indirectly responsible. We had three profuse hemorrhages early in our work but no instance of serious sequelae. Serous, hemorrhagic and purulent exudate occurred much too frequently while utilizing the galvanocautery of Jacobaeus. This and other disadvantages led me to perfect the instruments and adopt the high frequency method then widely applied in general surgery. Our first experience with the high frequency method, although superior to the galvanocautery, left much to be desired in the type of unit employed. When the Bovie Electrosurgical Unit* appeared on the market, with its new features for the control of bleeding, we tested it experimentally. Finding it fulfilled all requirements, we have since used it routinely, and attribute to the advantages of this unit our present low incidence of serous exudate (3.8 per cent), purulent exudate (2.5 per cent), and hemorrhagic exudate (1.2 per cent). Severe febrile reactions no longer occur.

The general conception of this operation is that only small adhesions, the size of one's finger, may be severed with safety. However, I have had repeated success in severing adhesions as large as the palm of the hand of an average man,—without hemorrhage or deleterious complications.

In a series of over 250 cases, 70 per cent have been clinically successful,—that is, the unsatisfactory collapse was converted into a satisfactory one and all patients were restored to working capacity with a negative sputum, whereas, before operation, over 90 per cent had a positive sputum and 85 per cent were bed cases.

Intrapleural pneumolysis is attracting the attention it justly deserves. Were it utilized to the extent it merits, fewer thoracoplasties would be performed on the class of cases wherein a pneumolysis is appropriate. We are convinced that three to five months' trial will determine the efficacy of a pneumothorax. If, after that period of time has elapsed, roentgenograms show evidence that adhesions are preventing closure of cavities, a thoracoscopic examination, which is as harmless as a pneumothorax refill, should be made to determine their operability. Adhesions found suitable for operation should be severed. If inoperable types are present, the useless pneumothorax should be discontinued and other surgical collapse procedures promptly put to use before the case is too far advanced.

PHRENIC NEURECTOMY

While intrapleural pneumolysis is the most neglected operative collapse procedure, one may reasonably state that phrenic neurectomy undoubtedly is the most abused. In 1912, Stuertz proposed resection of the phrenic

* Manufactured by The Liebel-Flarsheim Co., 303 West Third St., Cincinnati, Ohio

nerve to paralyze artificially the hemidiaphragm on the diseased hemithorax to provide functional rest of the lung. Resection of the nerve was followed by atrophy of the musculature of the diaphragm and its gradual rise into the thorax. Collapse of the lung, amounting to one-fourth to one-third its volume, took place.

The original operation was relatively short-lived, in approximately one-half to one-third of the cases, the diaphragm paralysis was of short duration or failed to occur at all. When the anomalies of the phrenic nerve became known, through the work of Felix and Goetze and confirmed by Plenk and myself, two operations were proposed—the exaeresis of Felix and the radical phrenicotomy of Goetze. Space does not permit a discussion of the merits of these two operations.

Based on the anatomical studies of Plenk and myself,⁵ the preferable approach to the phrenic nerve is through the subclavian triangle. One is thus in a position safely to evulse the nerve, as well as sever accessory nerve fibers, if encountered. It is unnecessary to remove the entire nerve, as we find that an 8 to 10 cm. length is sufficient to give a permanent paralysis.

Phrenic neurectomy is a minor operation, and while anomalies of the nerve exist in more than 25 per cent of cases, it is amazing that more complications do not occur. The operation should not be undertaken without a thorough knowledge of the topographical anatomy of the neck and familiarity with variations of the phrenic nerve. Ignorance of phrenic abnormalities is responsible for many accidents during operation, and fatal results have occurred even in the hands of competent surgeons. Damage to the vagus and sympathetic trunk is not uncommon,—also instances have been cited where no phrenic nerve was found. We, ourselves, have operated upon five patients who were referred to us after previous unsuccessful attempts by others to locate the phrenic nerve. In each case we found the phrenic nerve arising from the fifth cervical root far lateral to the scalenus anticus. A recent consultation had to do with a patient from whom a surgeon had removed a section of what was thought to be the phrenic nerve. The patient developed a Horner syndrome, but the diaphragm functioned normally. A second surgeon later reoperated upon the same case, and removed a section of a nerve—supposedly the phrenic—and the patient promptly exhibited a unilateral paralysis of the vocal cords. The diaphragm, however, still functioned normally. Certainly, such accidents should be avoided.

Indications The indications for phrenic neurectomy are

As an independent procedure in all cases wherein an artificial pneumothorax is indicated and attempts to introduce gas have proved futile or insufficient because of inoperable pleuritic adhesions which cannot be severed by the closed method of intrapleural pneumolysis, for social or economic reasons in cases when a prescribed course of pneumothorax is not possible.

Before every thoracoplasty because the improvement following an induced hemidiaphragmatic paralysis may be so marked as to avert the neces-

sity of a major surgical operation. A satisfactory hemidiaphragm paralysis (in favorable cases) occasions such improvement that the patient is rendered a far better surgical risk, also the sputum quantity and cough are markedly diminished, thus minimizing the danger of aspiration infection if a thoracoplasty is done. Its employment before thoracoplasty is also indicated since, by providing as much collapse as possible through the rising diaphragm, one may be able to reduce the number and length of ribs to be removed later. Through its use also the heart accommodates itself in stages to the increased functional activity that will be demanded of it as a result of thoracoplasty.

The value of phrenic neurectomy is indisputable as a supplement to artificial pneumothorax (for additional collapse) where non-operable adhesions are preventing a satisfactory lung collapse, and also as a test of the soundness of the contralateral lung. In cases with suspicious changes in the better lung, some surgeons are of the opinion that a phrenic neurectomy is of greatest value as a "test" operation before a thoracoplasty. Should the physical or roentgenologic findings increase after phrenic neurectomy, with exacerbation of fever, or other perturbing manifestations, an extrapleural thoracoplasty is absolutely contraindicated. Contradictory to this belief, close scrutiny of our material corroborates the affirmation that the result of a phrenic neurectomy as a "test" operation, cannot be accepted with complete confidence, since we have seen a contralateral lung lesion withstand the "test" operation, but exhibit activity after a thoracoplasty. We have also observed an essentially negative contralateral lung exhibit disease following the "test" operation, but pass through a complete thoracoplasty undamaged, although the diseased area in the contralateral lung was essentially the same before each procedure.

Other indications are threatened early oblitative pneumothorax where phrenic neurectomy is used combined with oleothorax to maintain collapse, and in the treatment of empyema occurring as a complication of pneumothorax where it serves to lessen the area of pyogenic membrane, also toward the end of a course of pneumothorax therapy in a case with an originally very extensively diseased lung, in order to diminish the capacity of the hemithorax so that it may accommodate a lung which has been shrunk by scar tissue changes—thus lessening the danger of reexpansion of excavated areas, secondary bronchiectasis, or retraction of heart and mediastinal contents.

Results The limits of this dissertation do not permit an analysis of our entire series of approximately 500 cases of phrenic neurectomy, performed according to the various indications and clinical types of cases. Exudative types of tuberculosis should be excluded, as this form seldom derives any benefit. The best results are obtained in the fibrocavicular and fibrocavicular cavernous cases (provided the cavities are not too large), who are candidates for a thoracoplasty. Our experience in this type of case has been extremely gratifying, as 15 per cent of cases selected for thoraco-

plasty, who had a phrenic neurectomy as a preliminary operation, have recovered, rendering the thoracoplasty needless. We have frequently remarked that cavities in the apex heal as a result of a phrenic neurectomy alone, provided a good diaphragm elevation is obtained. However, if the diaphragm pursues a horizontal course and is fixed by dense pleurodiaphragmatic adhesions, no benefit can be expected.

One should await maximum elevation of the diaphragm before proceeding with a thoracoplasty, the required time being from three to six months. If it is obvious that a phrenic neurectomy alone will not provide sufficient rest and collapse of the lung for healing to take place, one may proceed with the thoracoplasty, after waiting sufficiently long to observe its influence upon the integrity of the opposite lung.

EXTRAPLEURAL THORACOPLASTY

This operation should not be regarded as a last resort procedure. Such a mistaken conception is often responsible for delaying the operation until the patient becomes a bad surgical risk. There is urgent need of education regarding the role of thoracoplasty, for the impression that it is a shocking deforming operation, with high mortality and scant hope of cure, is a greatly mistaken one and should be rectified. In essentially stationary cavity cases with a good contralateral lung, if after a reasonable trial of the rest cure attempts to establish a pneumothorax have been prevented by adhesions, or if a pneumothorax has been established and adhesions of an inoperable type prevent closure of the cavity, and a phrenic neurectomy has not obtained the desired results, a paravertebral extrapleural thoracoplasty should be decided upon, provided there are no contraindications. The best results will be secured in chronic fibrous tuberculosis with evidence of shrinkage. If cavities are present, the thicker the wall, the less favorable will be the outcome.

The contraindications for thoracoplasty are the same as for an artificial pneumothorax, with the exception that disease of the contralateral lung, concerning which some leniency may be exercised in relation to a proposed pneumothorax, is an absolute contraindication to thoracoplasty unless it be arrested and not extensive. Poor surgical risks should be excluded, particularly if the operation is undertaken in a tuberculosis sanatorium, as the loss of a case is discouraging to others facing the same operation. The presence of incurable or uncontrollable organic disease is also a contraindication for thoracoplasty.

The selection of cases must be much more rigid than for pneumothorax. Exudative types of tuberculosis are unsuited for thoracoplasty, and patients whose resistance to tubercle bacilli invasion is inadequate, permitting progressive extension of disease, usually are poor risks. Limitation of operation to the age of 45 or 50 years is unnecessary if clinical and laboratory

studies indicate that the patient is a good surgical risk. Our oldest patient was 62, with tuberculosis of 15 years' duration. She made a perfect recovery.

A case with a combination pneumothorax, with a large cavity being held open by diffuse adhesions, would seem to offer an ideal indication for thoracoplasty. Yet, our experience suggests the contrary,—especially if there is a mediastinal bulge to the opposite side. Collapse of the chest wall increases the hernia, moreover, the presence of the pneumothorax often prevents a satisfactory collapse of the chest wall. The outcome in the above type of case can be greatly improved by artificially stiffening the mediastinum by precipitating a pleuritis of the bulge. The technic is simple and harmless. The patient is placed on the table with the pneumothorax side up, then, the second intercostal space is anesthetized as for a pneumothorax refill, and 2 c c of 1 per cent oil of gomenol and paraffin are slowly injected so that it will flow into the hernia. The patient remains in the same position for one-half hour, after which 50 to 100 c c of normal saline solution are slowly introduced through the same puncture, so that it will likewise flow into the bulge. The gomenol will now float upon the salt solution. Next, the patient is seated upright and the salt solution with gomenol is aspirated through another puncture at the base—this procedure prevents the formation of a diffuse pleuritis. With a normal pleura, a slight febrile reaction with exudate will occur, but it will be mild and will last only a few days. If there is no reaction, the procedure is repeated, using 2.5 per cent gomenol in the same manner. Again, if no reaction takes place, one repeats the process, gradually increasing the strength of gomenol until a reaction does occur. It may even be necessary to increase the strength up to 10 per cent. A successful issue is indicated by a gradual return of the mediastinum to the midline. This simple method of fixing the mediastinum also renders the patient a better surgical risk by eliminating the danger of mediastinal flutter. We avail ourselves routinely of this method in the last named type of case. This procedure should usually precede a thoracoplasty by two or three months, or even longer, and should also come before the preliminary phrenic neurectomy has been performed.

If the pneumothorax is a small one, it is better to permit the lung to expand before attempting the thoracoplasty.

I have no intention of going into the technic of thoracoplasty, but some of the essentials ought to be pointed out. Routinely, in the presence of underlying disease in the upper half of the hemithorax, we perform the upper phase first, contrariwise, if the pathologic lesions are chiefly in the lower lobe, we do the lower phase first. The operation should be done in two or more sittings. For poor risk patients, we prefer the graded thoracoplasty suggested by Hedblom.

The length of segments and number of ribs to be resected must be individualized in each case—depending upon the underlying lesion and the condition of the patient. Adequate sections of ribs should be severed close

to the transverse processes. In a number of cases operated upon by others as well as in some of our early cases, the sections of ribs removed were too short, the cavities remained open and the removal of regenerated rib became necessary. This latter procedure is an altogether unpleasant one, as the removal of portions of regenerated rib sufficient to provide adequate collapse is sometimes a tedious operation. Because of the above error, one of our early cases was operated upon nine times before the cavity was successfully closed.

When large upper lobe cavities are present in a case with a pneumothorax, we routinely follow the upper phase operation by an accessory lateral one, including the first rib, then proceed with the lower phase, unless only a partial thoracoplasty is intended. We feel that a much better collapse of large cavities is effected by the above sequence of operation. Partial thoracoplasties on upper lobe cavity cases have often produced disappointing results, necessitating reoperation to secure a better collapse.

According to our experience, if the case presents a large cavity extending to the second rib in front, and if the lung over the cavity is diffusely adherent to the chest wall while the rest of the lung is completely collapsed by a pneumothorax, the upper phase operation should be done first, resecting, if possible, substantial segments of the upper five ribs and all of the first. During the operation, a 14 gauge needle should be left in position through the chest wall so that, as the chest wall falls in, air may pass out of the pleural cavity. The needle must be kept away from the operative field and withdrawn after the operation is completed. Within a week or 10 days the remaining portions of the above ribs are resected close to the sternum through a midaxillary incision. Between operations a film will indicate the advisability of aspirating air before the second operation, but a needle is again placed in position during the second operation to allow air to escape. Within a week or 10 days, the lower phase operation follows with the needle again in position. Following the completed thoracoplasty, air is aspirated at regular intervals and the chest wall tightly strapped to obliterate the pneumothorax. The patient is placed in the author's thoracic hammock as soon as possible to effect a better chest wall collapse during the period of osteogenesis and to prevent deformity.

In performing a thoracoplasty in combination with a pneumothorax, or in cases with free pleural space, one should exercise great caution in stripping the rib of its periosteum so as not to tear through the pleura and possibly invert a bleeding intercostal vessel into the pleural cavity. In case of such an accident one should make sure that no bleeding vessel is inverted before closing the torn place. I once witnessed this accident in the hands of a very experienced and clever thoracic surgeon. Although all visible bleeding in the wound was arrested at the time of operation, the patient died several hours later. Autopsy disclosed the cause of death: hemorrhage into the pleural cavity.

After a thoracoplasty has been decided upon, the patient is prepared for operation. If he has spent months at bed rest and has normal temperature, it is advisable to have him sit up in a reclining chair, increasing the hours day by day until six hours have finally been reached. Then short walks are given—provided, of course, that febrile reactions do not take place. This plan improves the cardio-respiratory tone. Complete laboratory studies should be repeated, and blood transfusion given if indicated. Blood chemical studies, kidney function tests and an electrocardiogram should be made. The patient should be trained in cavity drainage, the time noted when this is completed,—and the hour of operation then scheduled for a time when the cavity is essentially empty. One week prior to operation the patient is placed upon a protein-free, carbohydrate-rich diet with abundant water, and hard candy is sometimes given after meals. He is also prepared psychically for operation, and 24 hours before the procedure, he is placed in an oxygen tent for one-half hour out of every three for purposes of hyperventilation. We are sure that this plan has contributed much to our low operative mortality.

Preoperative medication in nervous and apprehensive patients consists in luminal, oral sodium, or nembutal the night before operation to insure a good sleep. This medication may be repeated three hours before operation if necessary. One-half hour before operation we usually give $\frac{1}{3}$ grain of pantopon, if there is no idiosyncrasy. In good surgical risk cases, with normal blood pressure, we often administer pernoston or sodium amytal intravenously in hypnotic doses. The operation is performed under local anesthesia with 1 per cent novocain-suprarenin, and light ethylene anesthesia. During operation a constant check is made upon the blood pressure, pulse and respiratory rate, and the moment any suggestion of shock appears, the operation is concluded. Until a few years ago, we made an effort to perform the operation quickly, since then, we take more time—25 to 30 minutes if all goes well. After operation the patient is again placed in the oxygen tent for 24 hours as before operation. Intravenous transfusion of blood, saline solution or acacia is given if necessary.

Nurses with special training should be in charge of these cases to support the chest wall during coughing and at the same time encourage the patient to raise the required amount of sputum. If necessary, opiates are used to control pain during the first two days following operation.

Before the next operation the case is carefully studied and prepared. As soon as possible after the completed posterior operation, the patient is placed upon the operated side in the thoracic hammock³. The hammock is elevated from the bed, this increases the chest wall collapse and prevents deformity. Daily resting (for several hours) in the hammock is continued for three months, during which time the chest is kept tightly strapped.

We have experienced no death from postoperative shock, wound infection or hemorrhage in our series of 150 cases. Three postoperative deaths within a week were due to cardiac failure. The remaining fatalities were

due to aspiration pneumonia, progressive tuberculosis in spite of the operation, or to tuberculosis of the intestines and from other causes not related to operation

The results of a well performed thoracoplasty compare favorably with the results obtained from artificial pneumothorax. In our series of 150 cases upon whom 360 operations have been performed, the clinically well group totals 70 (46.6 per cent). The improved group comprises 36 cases (24 per cent). They are capable of working but tubercle bacilli are occasionally found in the sputum. No doubt half will recover. In nine (6 per cent) who still have a positive sputum it is probable that additional collapse will be necessary. Three (2 per cent) have died as a direct result of the operation from cardiac failure, 14 (9.3 per cent) died of causes indirectly due to operation, such as aspiration pneumonia, 18 (12 per cent) died of causes not related to the operation, such as intercurrent disease, accidents, etc.

The results of surgical treatment of pulmonary tuberculosis are stimulating, and it is extremely gratifying to know that every tuberculosis sanatorium or hospital where tuberculosis is accepted has a number of patients who can be restored to health and self-support by the application of modern thoracic surgery, instead of being left to await a certain dissolution of soul and body.

There has been a gradual awakening on the part of those accepting the responsibility for the treatment of pulmonary tuberculosis to the fact that collapse therapy, particularly surgery, offers a hope unattainable by the routine sanatorium regimen. The application of collapse therapy to the fullest extent that it is indicated would be facilitated by better cooperation between the medical tuberculosis specialist and the thoracic surgeon, in institutions where a strictly medical and surgical service exists, and requires transfer of cases for operation from one service to the other. The ideal situation exists when the phthisiotherapist is qualified by training and experience to assume entire responsibility from both the medical and surgical standpoint so as not to necessitate, as it were, the changing of pilots in midstream. Successful collapse therapy, similar to urology, laryngology, and gynecology, is largely a one-man job. I predict that the tuberculosis specialist of the future will have both adequate medical and surgical training to conduct the treatment of pulmonary tuberculosis according to the indications and will not, as is now often the case, call in the thoracic surgeon when the case has become too far advanced for surgical relief.

The material referred to in this contribution is from the combined service of myself and associates, Dr Ray W. Matson and Dr Marr Bisailon.

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OBSERVATIONS ON THE DIAGNOSIS AND TREATMENT OF PERIPHERAL VASCULAR DISEASE*

By EUGENE M LANDIS, *Philadelphia, Pennsylvania*

For the diagnosis, prognosis, and effective therapy of peripheral vascular disease it is essential to divide patients into two groups (a) those whose symptoms are due to simple spasm with no, or at most slight, organic vascular obstruction, and (b) those whose symptoms are due primarily to advanced organic disease of the arteries. Recent advances in the surgery of the sympathetic nervous system have made it highly desirable to detect early in the course of peripheral vascular disease, whether the flow of blood to an extremity is diminished by simple arterial spasm, or by obliterative structural disease of the arteries. In treatment the best results can be obtained only if beginning organic occlusion is discovered before it has reduced too greatly the normal capacity of the blood vessels to dilate.

The several tests available for detecting early organic vascular obstruction, though different in method, are similar in principle. The surface temperature of the cold, exposed extremity is measured thermoelectrically. Vasoconstrictor tone is then abolished in the part under observation and the rise in surface temperature is recorded. The level to which skin temperature rises during complete vasodilatation has been determined in persons with normal peripheral circulation. If the surface temperature fails to reach this normal level in a room at suitable temperature, it can be concluded that the arteries supplying the part are unable to dilate owing to organic changes in their walls.

Vasodilatation of the peripheral vessels may be induced by many procedures, but we have chosen to use the simple expedient of immersing two extremities in warm water^{1,2} verifying abnormal findings in most instances by anesthetizing the posterior tibial nerve³. In completely normal subjects immersing the forearms for 35 minutes in water at 43 to 45° C dilates the cutaneous vessels of the lower extremities and elevates the surface temperature of the toes to 31.5° C or more. Conversely, immersing both feet and legs in warm water for 35 minutes normally elevates the surface temperature of the fingers to 31.5° C or more.

Patients with coldness, blueness or pain in the lower extremities who show under suitable conditions a normal elevation of skin temperature (ie to 31.5° C or more) are certainly free from significant organic arterial obstruction (figure 1). When skin temperature fails to reach 31.5° C but still reaches 26° C or more (figure 2) only a moderate grade of organic occlusion is present. In such patients considerable benefit can be expected from contrast baths, local heat, diathermy, vasodilator drugs, the warm

* Read at the Chicago meeting of the American College of Physicians, April 16, 1934.
The expenses of this study were defrayed in part by a grant from the Philadelphia Heart Association.

cradle or sympathetic ganglionectomy, all of which increase blood flow, temporarily or permanently, by dilating those vessels which are still capable of expansion

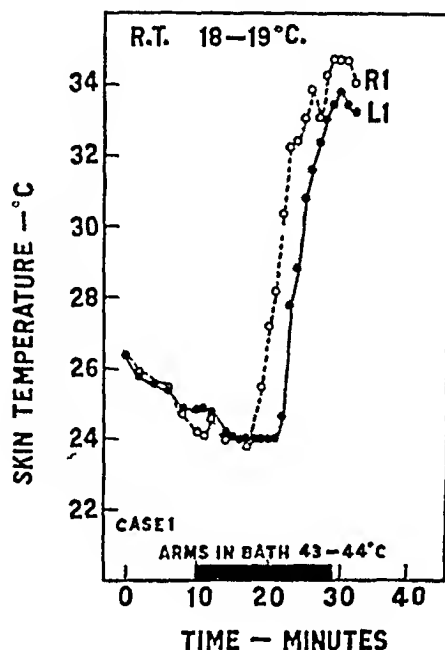


FIG 1 Normal vasodilator response observed in a patient with bilateral thrombophlebitis. In this and subsequent charts L1 and R1 indicate the skin temperature of the left and right great toes, respectively, R T, the room temperature. The shaded area below indicates the period during which the forearms were immersed in warm water. (From Landis and Gibbon,² by permission of the *Archives of Internal Medicine*)

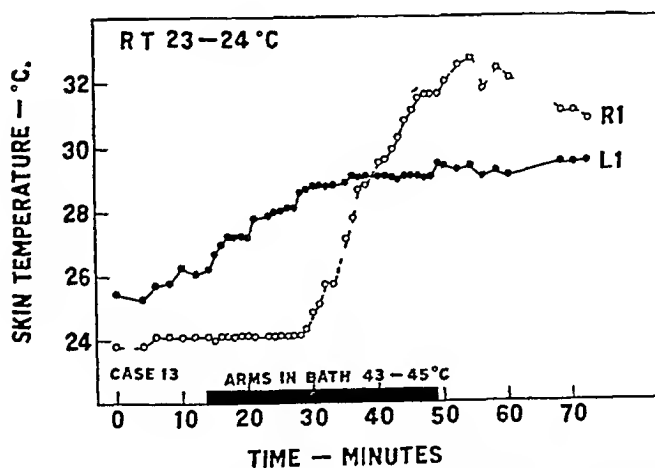


FIG 2 Vasodilator response in a patient with arteriosclerosis. The response was only partial in the left foot and was much delayed in the right foot. (From Landis and Gibbon,² by permission of the *Archives of Internal Medicine*)

In the advanced stages of peripheral vascular disease the arteries become more or less rigid owing to structural changes in their walls. These diseased vessels have not only abnormally small lumina but they may be unable

to dilate even when vasoconstrictor tone is abolished. Skin temperature then fails to rise (figure 3) during the period when vasoconstrictor tone is

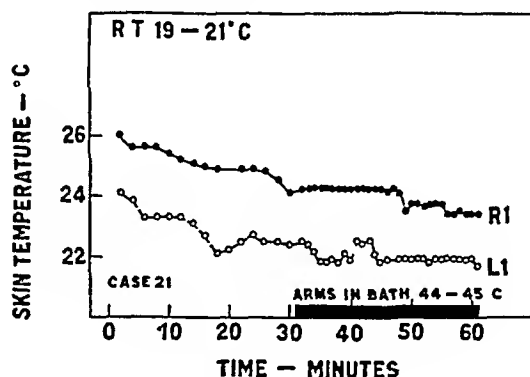


FIG. 3. Chart showing complete absence of vasodilator response in a patient with advanced diabetes and arteriosclerosis with gangrene. (From Landis and Gibbon,² by permission of the *Archives of Internal Medicine*.)

abolished. After the arteries have thus lost their power of dilating, the therapeutic procedures mentioned previously cannot be expected to increase blood flow and, in fact, they usually fail to improve the nutrition of the tissues in the extremity. Eventually many of these patients with conspicuous organic occlusion suffer from trophic changes, ulceration and gangrene, leading finally to amputation. Such patients present a particularly harassing therapeutic problem since the usual methods of increasing peripheral circulation all depend fundamentally upon the residual power of vasodilatation. At the University of Pennsylvania we have been interested during the past three years in the problem of attempting to increase peripheral blood flow in this unfavorable group of patients. It can be expected that any procedure which increases blood flow in spite of advanced organic occlusion will reduce pain, aid healing, and delay or possibly prevent the appearance of gangrene. Rest pain and ulceration frequently require the amputation of extremities which, if they could be preserved, would prevent the patient from becoming an economic liability.

Poiseuille, early in the last century, described the laws which control the flow of fluid through a rigid tube. He observed that the amount of blood flowing through a capillary tube depends upon the fall in pressure along the tube. This relationship can be demonstrated clearly in the living animal by measuring simultaneously capillary blood pressure and the rate of blood flow in single capillaries of the frog's mesentery.⁴ Inserting a minute glass pipette into a single capillary makes it possible to follow the variations in capillary blood pressure which result from spontaneous arteriolar dilatation and constriction. Though capillary blood pressure varies considerably, venous pressure remains approximately constant. The drop in pressure from the capillary to the vein, represented in figure 4 by the shaded vertical columns, can be at one moment very small, at another quite

large The rate at which blood flows through the observed capillary follows faithfully each variation in capillary blood pressure In other words, when capillary and venous pressures are equal the drop in pressure along the capillary is minimal and blood flow ceases On the contrary, when the drop

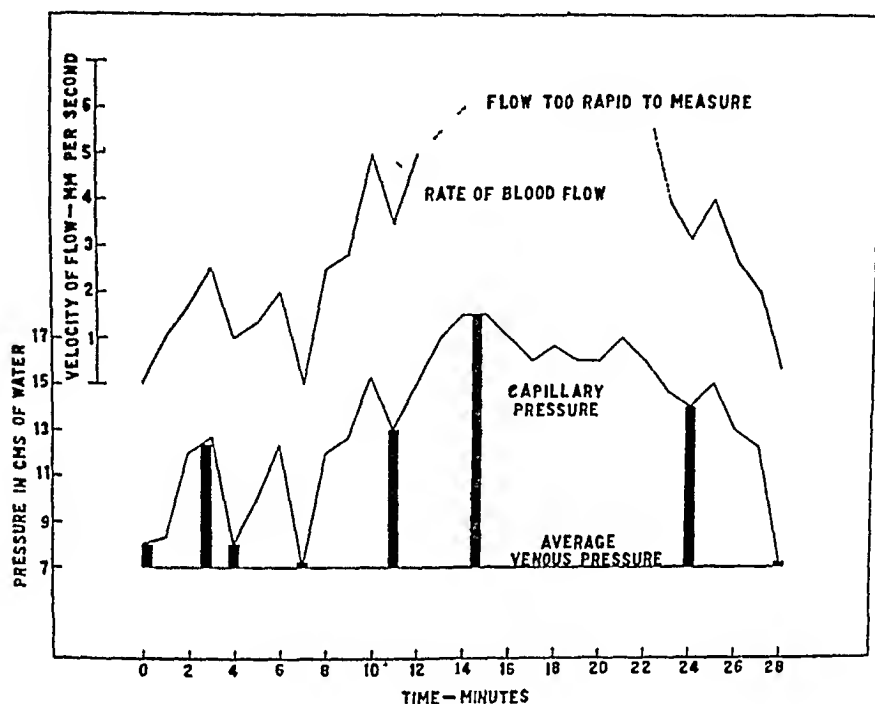


FIG 4 Showing relation between capillary blood pressure and the rate of blood flow in a single capillary of the frog's mesentery (From Landis,⁴ by permission of the *American Journal of Physiology*) The vertical shaded areas represent the drop in blood pressure from capillary to vein

in peripheral blood pressure is large, flow may become too rapid to measure microscopically Thus, it may be expected that, if the peripheral drop in blood pressure be increased artificially, blood flow may be made greater

In the presence of a rigid system of arteries, incapable of dilatation, the total fall in pressure in the peripheral vascular system may be increased in two ways, (a) by elevating systemic blood pressure, or (b) by diminishing venous pressure The first method is generally impracticable for numerous and obvious reasons It seemed possible, however, that applying negative pressure periodically to the skin of the extremity might increase blood flow by temporarily reducing venous pressure below atmospheric pressure

An aluminum box was built large enough to accommodate the lower extremity to a point six inches above the knee where the thigh was surrounded by an air-tight rubber cuff (figure 5) An air pump, valve, mercury manometer, and relay were so arranged that the lower extremity was exposed alternately and automatically to a negative pressure of 80 to 120 mm Hg for 25 seconds and a positive pressure of 60 to 80 mm Hg for five

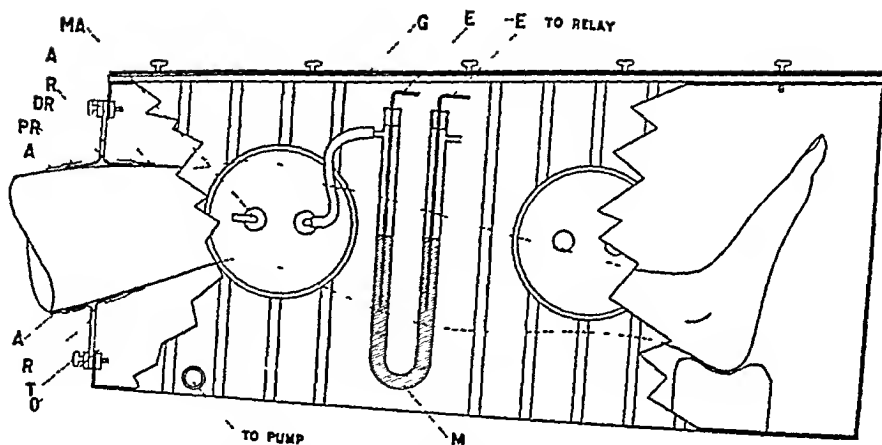


FIG 5 Diagram of aluminum box and double cuff (PR, DR) used for applying suction and pressure to the surface of the lower extremity (From Landis and Gibbon,⁶ by permission of the *Journal of Clinical Investigation*)

seconds Figure 6 indicates diagrammatically the rapidity with which pressure is changed, only 3 seconds being required for the shift from +80 mm Hg to -120 mm Hg. The normal difference between mean arterial and venous blood pressures is about 80 mm Hg. During suction this peripheral drop in blood pressure (vertical shaded areas in figure 6) is

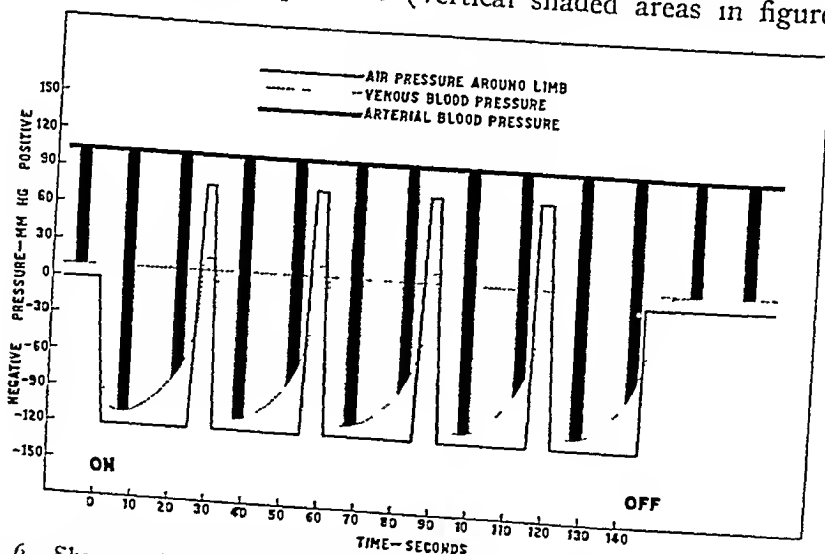


FIG 6 Showing diagrammatically (a) the duration of the alternate periods of suction and pressure, and (b) the rapidity with which the changes in pressure are accomplished

considerably increased. The skin becomes red as the capillaries and veins are filled with blood. To empty the capillaries and veins rapidly at the end of 25 seconds of negative pressure, air is pumped rapidly into the box and pressure is elevated within three seconds to +80 mm Hg. The skin

blanches and the vessels are emptied through the veins to afford a reservoir into which fresh arterial blood may be drawn by the next period of negative pressure. The net result of this alternating suction and pressure is to increase considerably the average drop in blood pressure from artery to vein. Theoretically this should increase proportionately the flow of blood through the peripheral vessels of the extremity.

Prolonged ischemia produces local coldness, cyanosis, intermittent claudication, rest pain, and eventually ulceration or necrosis of tissue. If it is true that suction and pressure increase the local supply of arterial blood, these manifestations of ischemia should be relieved, at least to some degree. Landis and Gibbon^{5,6} showed in normal subjects under carefully controlled temperature conditions that blood flow, as indicated by skin temperature, was greater in the limb exposed to pressure variations. It was concluded that to obtain maximal effects on blood flow it is advisable to have (1) relatively brief periods of suction, (2) intermittent brief periods of pressure, and (3) diminished vasoconstrictor tone, the last being necessary in order that the reservoir for accommodating blood drawn in by each suction period might be adequate.

This paper comprises a brief summary of the effects of suction and pressure on the various manifestations of reduced blood flow in a series of 16 patients with advanced peripheral vascular disease. The disease was, in each instance, of long standing, the patients suffered from thromboangitis obliterans, simple arteriosclerosis, or diabetes with arteriosclerosis. Twelve of these patients had no vasodilator response in the observed extremity, while the remaining four showed in the most severely involved extremity a rise of skin temperature to between 24 and 27° C.

With the patient semi-recumbent, the most severely involved extremity was exposed to pressure variations for periods of one to two hours, from twice daily to once weekly, for totals of 2 to 112 treatment hours. Suction was between -80 and -120 mm Hg, pressure between +60 and +80 mm Hg. Suction and pressure were applied alternately for 25 and 5 seconds, respectively, except in one instance in which intervals of 50 and 10 seconds were used for part of the time (Table 3, Patient C3). When skin temperatures were measured conditions were carefully controlled as described previously.⁶ Vasoconstrictor tone was reduced by enclosing one forearm in an electric heating pad kept warm enough to produce slight generalized sweating.

Table 1 presents a summary of a series of short observations on the effects of suction and pressure on skin temperature. In every instance the foot which was exposed to pressure variations became warmer than the control extremity. The final temperature reached was always above that attained by the extremity when maximal vasodilatation was produced by abolishing vasoconstrictor tone. The digits of the foot exposed to suction and pressure became, on the average, almost 6.0° C warmer than the untreated, or control, digits. The smallest difference in temperature was

TABLL I

The Effects of Suction and Pressure on Skin Temperature in Patients with Peripheral Vascular Disease

| Patient No | Side | Vasodilator response | Duration of application of suction and pressure | Temperature of digits | | Rise in temperature |
|------------|------|----------------------|---|-----------------------|-----------------|---------------------|
| | | | | Before treatment | After treatment | |
| 1 | R | none | min 59 | ° C 22.2 | ° C 30.5 | ° C 8.3 |
| | L | none | none | 21.0 | 23.6 | 2.6 |
| 2 | R | none | none | 23.5 | 27.0 | 3.5 |
| | L | none | 111 | 20.7 | 30.2 | 9.5 |
| 3 | R | to 24° C | 81 | 19.4 | 31.9 | 12.5 |
| | L | to 26° C | none | 19.8 | 22.5 | 2.7 |
| 4 | R | none | 41 | 24.4 | 28.1 | 3.7 |
| | L | none | none | 24.3 | 25.8 | 1.5 |
| 5 | R | none | 27 | 26.3 | 30.3 | 4.0 |
| | L | none | none | 30.3 | 29.8 | -0.5 |
| 5 | R | to 30° C | none | 26.0 | 26.2 | 0.2 |
| | L | to 27° C | 120 | 25.8 | 31.8 | 6.0 |
| | R | to 30° C | none | 21.5 | 24.2 | 2.7 |
| | L | to 27° C | 120 | 21.8 | 30.9 | 9.1 |
| | | | Average | Treated extremities | | 7.6 |
| | | | | Untreated extremities | | 1.8 |

22° C (Patient 3), the largest 98° C (Patient 2). The difference between the skin temperatures of the treated and untreated extremities was usually large enough to be perceptible to the hand of the examiner, and to the patient himself.

Skin color was estimated according to the Lewis⁷ scale in which XV and XVI correspond to complete cyanosis, V to bright hyperemia, and VII or VIII to normal skin color. In areas of frank gangrene (table 2) no change in color could be detected, probably since the affected vessels were already thrombosed and circulation was at complete standstill. The digits of patients with severe pain, with or without ulceration, were more or less cyanotic. In some it required but a few alternations of pressure to change this cyanosis to normal skin color. The skin then became deeply red during suction and pale during pressure as does normal skin. Small areas remained cyanotic for several days, but the normal coloration eventually

TABLE II

Effects of Suction and Pressure on Skin Color in Patients with Peripheral Vascular Disease

A With areas of frank gangrene

Patient 1 No definite color changes XV

2 No definite color changes XV

3 No definite color changes near lesion XVI-XV Remote areas of skin XII to X

4 Doubtful changes near lesion XV Other areas XI to VII

B With indolent, painful ulcers but no frank gangrene

Patient 1 XII to VII

2 XIII to VII

3 IX to VII

4 IX to VII

5 XI to VIII

6 XIII to VII

7 XIII to VII

C With pain alone

Patient 1 XII-XIII to VIII

2 XIV to VIII

3 XII to VII

4 X-XIV to VII-VIII

extended over the whole skin surface. The hyperemia produced during the first few alternations in pressure is maintained for some hours, and usually becomes more and more lasting as treatment continues. In some, however, cyanosis persisted in the intervals between treatments. In three instances striking improvement in skin color has been followed during the winter and has remained in spite of severe cold.

Most of these patients suffered also from severe and often intractable rest pain, which was either constant or occurred in brief episodes, usually worse at night. Two types of observations may be summarized. First, to observe acute effects extremities were exposed to pressure variations during episodes of pain. Protocols 1 and 2 indicate the relief of pain.

ACUTE EFFECTS OF SUCTION AND PRESSURE ON REST PAIN

Protocol 1 Patient had thromboangitis obliterans with large gangrenous slough in palm following amputation of finger in another hospital. Patient was unable to keep hand above the level of the sternum owing to excruciating rest pain.

12 15 p.m. Pain present. Hand placed above level of sternum in modified box. Suction (80 mm Hg) and pressure (60 mm Hg) applied for 25 and 5 seconds, respectively.

12 30 p.m. No pain.

1 45 p.m. No pain,—pump stopped for 2 minutes. Severe pain in palm.

1 47 p.m. Pump started again.

1 48 p.m. Pain less.

1 49 p.m. Pain gone,—itching remains.

2 30 p.m. Hand removed from box. Pain recurred after patient returned to ward.

Protocol 2 Patient had arteriosclerosis and ulceration of two toes with rest pain preventing sleep in spite of sedatives.

| | |
|----------------|--|
| 11 00 p m | Severe pain wakened patient |
| 11 45 p m | Pain still present Patient placed in apparatus with suction (120 mm Hg) and pressure (80 mm Hg) for 25 and 5 seconds, respectively |
| 12 midnight | Pain gone, patient drowsy |
| 12 50-4 15 a m | Patient sleeping |
| 4 15 a m | Leg removed from apparatus Patient slept remainder of night |

obtainable The first patient was unable to keep the hand higher than the sternum owing to severe rest pain At 12 15 p m, when pain was present, the hand and forearm were placed in the apparatus so that they lay in a position known to produce pain Fifteen minutes after pressure variations had begun the pain disappeared although holding the hand in the same position was unbearable under ordinary conditions The pain remained absent until 1 45 p m when the pump was stopped for two minutes This was followed by severe pain in the palm Starting the pump again caused the pain to disappear leaving only some residual itching Pain was absent for the remaining hour of the observation The pain returned, however, several hours after suction and pressure were discontinued, and amputation was done primarily on account of the size of the slough Another patient (protocol 2) had ulceration with severe rest pain due to arteriosclerosis This pain had prevented sleep, in spite of moderate sedation, in the hospital At 11 00 p m severe pain wakened the patient, the affected extremity was placed in the apparatus at 11 45 p m, while pain was still present Fifteen minutes later the pain had disappeared and the patient was drowsy Thereafter he slept until 4 15 a m, when he was removed from the apparatus and continued sleeping during the remainder of the night

In the many hours during which extremities have been exposed to these pressure variations true rest pain has not been observed during treatment Discomfort sometimes appeared owing to drying of ulcers This can be avoided by covering the raw surfaces with vaseline As a rule patients, previously exhausted by continued pain, fall asleep almost immediately after the extremity is placed in the apparatus The continuous application of negative and positive pressure over long periods of time was attempted It was found quite early, however, that the rubber cuff at the proximal end of the apparatus became uncomfortable usually after two to four hours, making it impossible to prolong pressure variations uninterruptedly beyond this period

While temporary relief of pain was obtained even when areas of frank gangrene were present, pain returned more or less quickly after the limb was removed from the apparatus, as indicated in protocol 1 and table 3 Eventually amputation was performed in all four patients with frank gangrene (table 4) Three of this group were treated only a few hours, the totals ranging from 2 to 11 hours The fourth patient was treated for a

TABLE III

Prolonged Effects of Suction and Pressure on Pain of Vascular Type

| | | | |
|---|---|--------------------------------------|----------------------|
| A With frank gangrene or large, sloughing ulcer | | | |
| Patient 1 | Temporary relief (only 6 hours' treatment) | Amputation of arm | |
| 2 | Little, if any, relief (only 3 hours' treatment) | Amputation of leg | |
| 3 | Conspicuous, but temporary, relief required to heal indolent, painful ulcer at site of amputation | Amputation of toe | Suction and pressure |
| 4 | Conspicuous, but temporary, relief | Central slough enlarged slowly | Amputation of leg |
| B With indolent or slowly enlarging ulcers, and minor slough | | | |
| Patient 1 | Almost complete relief | | |
| 2 | Complete relief | | |
| 3 | Complete relief | | |
| 4 | Complete relief | | |
| 5 | Almost complete relief | | |
| 6 | Complete relief | | |
| 7 | Complete relief | | |
| C With intermittent claudication both with and without ulceration | | | |
| Patient 1 | Originally walked $\frac{1}{4}$ block | Stopped at 2 blocks by untreated leg | |
| 2 | Originally walked $\frac{1}{2}$ block | Increased to 10-12 blocks | |
| 3 | Originally walked $\frac{1}{3}$ block | Increased to 1 block | |
| 4 | Originally walked $\frac{1}{2}$ block | Increased to 2 blocks | |
| 5 | Originally walked $\frac{1}{4}$ block | No effect (only 3 hours' treatment) | |
| 6 | Originally walked $1\frac{1}{3}$ blocks | Increased to 10-12 blocks | |

TABLE IV

Effects of Suction and Pressure on the Healing of Indolent or Enlarging Ulcers Associated with Peripheral Vascular Disease

I Patients with local gangrene

| Diagnosis | Size of ulcer | Course | Effect |
|-----------------------------|--------------------------------------|--------|-----------|
| 1 Thromboangitis obliterans | Gangrenous slough 5 × 6 cm | Acute | None |
| 2 Thromboangitis obliterans | Gangrenous area 1 × 2 cm | Acute | None |
| 3 Arteriosclerosis | 2.5 × 2.2 cm Large central slough | Acute | Temporary |

II Patients with ulcers but without frank gangrene

| | | | |
|------------------------------|--------------|----------------------|---------|
| 1 Thromboangitis obliterans | 1.0 × 1.5 cm | (Indolent-1 month) | Healed |
| 2 Arteriosclerosis | 1.0 × 0.9 cm | (Acute) | Healed |
| | 0.7 × 0.8 cm | | Healed |
| 3 Arteriosclerosis, diabetes | 2.0 × 1.1 cm | (Indolent-3 months) | Healing |
| 4 Arteriosclerosis | 1.2 × 1.4 cm | (Indolent-4 months) | Healed |
| | 1.0 × 3.0 cm | | Healed |
| 5 Thromboangitis obliterans | 1.0 × 1.2 cm | (Enlarging) | Healed |
| 6 Thromboangitis obliterans | 0.8 × 1.0 cm | (Indolent-3½ months) | Healed |
| 7 Thromboangitis obliterans | 0.8 × 0.9 cm | (Indolent-5 months) | Healed |

total of approximately 50 hours with conspicuous, but only temporary, relief, amputation was eventually necessary

Patients with indolent or slowly enlarging ulcers, but without frank gangrene, large sloughs or extending necrosis, often obtained striking relief from rest pain. Sleep ordinarily became possible without sedatives after a few days. The results in patients with intermittent claudication were difficult to estimate and have been less striking, though in general slow improvement was observed. The subjective nature of the symptoms and the possibility of spontaneous recovery make it advisable to reserve judgment.

The diminished blood flow of peripheral vascular disease leads eventually to local gangrene, or to indolent ulceration which is resistant to treatment. Patients with frank gangrene did not improve significantly during or after exposure to pressure variations (table 4). One patient with a large sloughing ulcer under the malleolus showed temporary improvement, but very slow extension of the slough and continued pain made amputation eventually necessary. Those patients who had indolent ulcers without frank gangrene were markedly improved. The ulcers had, in some instances, been indolent or enlarging under treatment with antiseptics and heat for periods of several

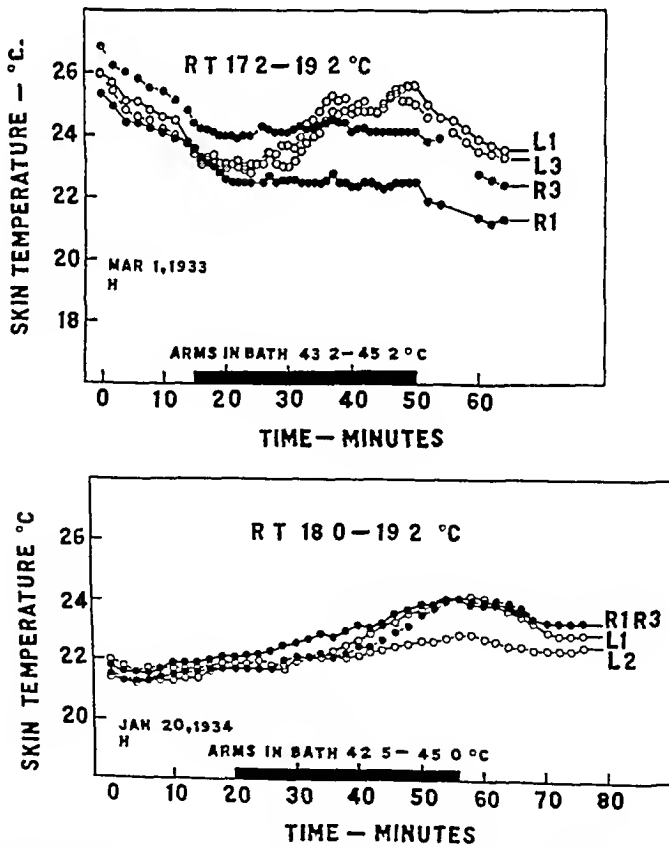


FIG 7 Showing slight improvement of vasodilator response (right lower extremity) in a patient with thromboangiitis obliterans after prolonged use of suction and pressure

months before pressure variations were used. The healing, which occurred during application of suction and pressure, was accompanied by improvement of skin color and diminution of rest pain.

The rise in skin temperature, the improvement of skin color, the diminution of rest pain and the healing of previously indolent ulcers indicate that alternate suction and pressure increases blood flow at least temporarily. At the present time it is impossible to do more than speculate upon the permanence of this improvement. Complete and lasting recovery depends upon the development of adequate collateral circulation. Sufficient time has not elapsed to determine to what extent increased blood flow depends upon the continued use of pressure variations.

In some patients collateral circulation develops slowly during and after treatment. Figure 7 illustrates observations on a patient in whom no response was observed during March 1933 in the right lower extremity. After the use of suction and pressure the right extremity showed during January 1934 a slight, but definite, increase in temperature during the immersion of forearms in warm water. The untreated extremity, on the contrary, exhibited on the second examination less vasodilator response than before. The patient illustrated in figure 8 showed no change in vasodilator response between February 1932 and March 1934 although considerable treatment was given during late 1933 and early 1934. Clinical improvement was distinct, however, rest pain and cyanosis disappeared almost completely, and an indolent ulceration following amputation healed without incident during the use of negative and positive pressure. The patient is at present ambulatory and able to work.

From the results summarized above it may be concluded that alternate suction and pressure increase blood flow temporarily, even after organic vascular disease has diminished, or abolished, vasodilatation. The changes of skin color, the alleviation of rest pain, the accelerated healing of indolent ulcers amplify the earlier evidence based on studies of skin temperature^{5,6}. Concerning the real therapeutic value of this procedure little can be said until a large series of carefully controlled and extensive clinical observations have been made. Reid and Herrmann have described the development of collateral circulation in patients with peripheral vascular disease after prolonged treatment by means of pressure variations in cycles of five minutes. They utilized at first⁸ Bier's method in which negative pressure was applied very gradually for two minutes, maintained at -70 mm Hg for one minute and then gradually relieved during two minutes, no positive pressure being used. More recently they⁹ have adopted a procedure involving briefer periods of negative pressure alternating with positive pressure in cycles as short as 15 seconds.

Contraindications to the use of suction and pressure can be given at this time on theoretical grounds only. Active or acute infection may well be unfavorably influenced by the procedure. Osteomyelitis, however slight, makes it unlikely that complete healing of cutaneous lesions can be obtained.

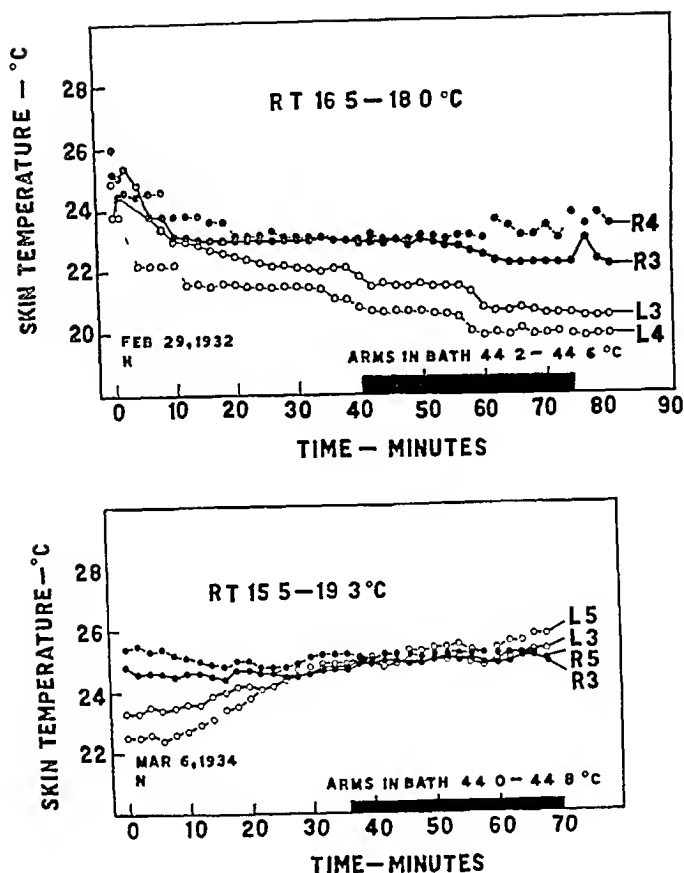


FIG 8 Showing no change in vasodilator response of patient with thromboangitis obliterans (subacute type) after the use of suction and pressure. Pain and cyanosis were much improved but blood flow was not sufficiently affected to change skin temperature when vasoconstrictor tone was diminished.

as long as drainage from beneath continues. When large masses of tissue are actually gangrenous, or sloughing, only temporary relief has so far been observed.

SUMMARY

It is necessary to detect beginning organic obstruction as early in the course of peripheral vascular disease as possible, since the therapeutic measures available depend to a large degree upon the ability of the blood vessels to dilate. Unfortunately, many patients reach the hospital after peripheral vascular disease has advanced to the stage when the arteries are no longer able to increase their diameter, though vasoconstrictor tone is entirely abolished. Even under these unfavorable conditions, however, it is still possible to increase blood flow by means of alternate suction and pressure. This procedure elevates skin temperature conspicuously, tends to relieve cyanosis, diminishes rest pain and favors, at least temporarily,

the healing of superficial, indolent ulceration. Whether or not the development of collateral circulation can be so stimulated as to return tissue nutrition permanently to a normal state is not yet certain. The practical importance of suction and pressure in the treatment of peripheral vascular disease will necessarily depend to a great extent on the degree to which collateral vessels take over the function of those arteries which are closed by disease. There are indications that even if the patient can only be aided temporarily over crises of rest pain or ulceration, time will be gained for the natural development of collateral circulation so that a certain number of mutilating operations can be avoided.

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THE ETIOLOGY OF ARTERIAL HYPERTENSION¹

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THE two questions most frequently asked of investigators engaged in the study of arterial hypertension are (1) how do you treat patients with arterial hypertension, and (2) what is the cause of arterial hypertension? The answers to these closely related questions are always given with embarrassment and humility. The answer to the first question is relatively simple, for there are but few therapeutic measures the beneficial nature of which is proved to be specific. The answer to the second question, which I intend to consider here, is difficult and at best incomplete.

Extensive and reliable experimental data are available indicating that arterial hypertension may be induced in animals in several ways. In addition, observations on patients with arterial hypertension have disclosed numerous alterations in the physiological and chemical functions. It is because of the many possible ways of inducing experimental hypertension, and because of the numerous deviations in bodily functions associated with hypertension, that the study of the etiology of *clinical* hypertension is so difficult. What we desire to know is the cause of arterial hypertension as it exists *in man*. The fallacies most frequently encountered in the solution of this problem are (1) generalizations from experimental observations in animals, without proper appreciation of the clinical problems, (2) an inadequate clinical study of the patient as to the type of arterial hypertension and as to its secondary complications, (3) the frequent misinterpretation of a finding which coincides with or is the result, rather than the cause, of arterial hypertension, (4) the inaccuracy of the methods applied.

Data bearing on the etiology of arterial hypertension have accumulated so rapidly during recent years that unless one has had experience in investigating the varied aspects of the problem one is completely lost in the maze of data. With a full realization that the problem is far from being settled, I shall present a viewpoint based on a critical analysis of the literature and on some personal experience.

The main lines of approach to the problem may be divided into the following groups: (1) the role of circulating substances, including hormones, (2) the influence of the nervous system, (3) the reactivity of the vascular system and mechanical factors, (4) infections and allergy, and (5) constitutional factors.

¹ Read at the Chicago meeting of the American College of Physicians, April 18, 1934. From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1 THE RÔLE OF CIRCULATING CHEMICAL SUBSTANCES IN ARTERIAL HYPERTENSION

This approach to the etiology of hypertension is perhaps the most obvious, particularly since examples of hormones with a vasoconstrictor effect are available. The search for chemical substances in the blood and in the urine actually goes back to the first clinical concepts of nephritis established by Bright and Johnson. It would be useless to enumerate here investigations of all the substances held responsible for the development of arterial hypertension. It is clear from the literature that glucose, salt, purine and protein substances are not etiological agents. Among the chemical theories which have interested investigators in recent years, there are several of particular interest.

Guanidine The first is that of Major^{2,3,4} who proposed that retention of guanidine bases is responsible for essential hypertension. In support of his assertion he has demonstrated that administration of certain guanidine compounds produces a rise in the blood pressure of experimental animals, and has claimed that in patients with essential hypertension the excretion of guanidine bases in the urine is diminished, and the guanidine content of the blood increased. Major's contention cannot be considered valid at present (1) because the amounts of guanidine compounds administered to animals are relatively large, and (2) particularly because the reliability of the chemical methods which he used for the demonstration of guanidine bases in the blood and urine is questionable^{5,6}. Kleeberg,⁷ using a colorimetric method similar to that used by Major, has observed an elevation of the guanidine content of the blood in patients without hypertension. In patients with hypertension, he found that the guanidine content was elevated only when there was an accumulation of protein derivatives and products of intestinal putrefaction; in a number of cases he observed normal colorimetric values. Turriès and Robert⁸ and likewise Jackson⁹ in our clinic were unable to establish a correlation between hypertension and the guanidine content of the blood. It should be remembered that more recent experiences with creatinine and urea clearance tests indicated that an impaired excretion of some compounds may occur in patients with hypertension without necessarily bearing on the etiology of the condition.

Cholesterol Schmidtman¹⁰ has observed a temporary elevation of the blood pressure in rabbits following prolonged cholesterol feeding. Westphal,¹¹ on feeding rabbits a high cholesterol diet, observed that their blood pressure rose concomitantly with an increase in the serum cholesterol. Investigating a series of 80 cases of essential hypertension, he also found that the cholesterol level was above the normal range in 71 per cent of the cases. Weil and Guillaumin¹² and Askanazy¹³ found high cholesterol values in the plasma of patients with hypertension. Thus, on the basis of observations on man as well as of experiments on animals, Westphal and others consider cholesterol as one factor in the genesis of essential hyper-

tension Although the experimental work of Schonheimer,¹⁴ Shapiro¹⁵ and Tholldte,¹⁶ and the chemical studies in man of Mjassnikow,¹⁷ Loewenstein,¹⁸ Harris and Lipkin¹⁹ have shed much doubt on the rôle of cholesterol in the production of arterial hypertension, we²⁰ reinvestigated this problem in 75 cases of hypertension Our study revealed that patients with secondary renal complications were more apt to show hypercholesteremia than were those with secondary cardiac involvement On the other hand, of 37 patients with uncomplicated hypertension, only five showed an unexplained hypercholesteremia We have therefore concluded that the elevation of cholesterol is the result, rather than the cause, of changes in the cardiovascular system in arterial hypertension

Potassium-Calcium Ratio Since experimental observations^{21, 22, 23, 24} suggest that changes in sympathetic-parasympathetic and potassium-calcium balance can be detected by their effect on the action of hormones, Kylin²⁵ investigated the relation between the reaction to epinephrine and the potassium-calcium ratio He observed that in cases with a potassium-calcium ratio of from 0.7 to 2.15, which is within his normal range, there were normal reactions to epinephrine The blood pressure curve of patients with essential hypertension having a ratio over 2.15 was consistently vagotonic, that is, the patients exhibited a fall in blood pressure after epinephrine Kylin, Brenms²⁶ and Loewenstein¹⁸ found a definite rise in potassium content in cases of essential hypertension, while calcium values were either at, or below, the lower limits of normal Jansen²⁷ found that in patients with arterial hypertension, with or without renal involvement but without cardiac failure, the calcium values were at the lower level of the normal range Stieglitz²⁸ investigated 47 cases of pregnancy, with arterial hypertension as a secondary complication He found that the average calcium value in his pregnant patients coincided with that in his controls, and therefore he concluded that hypocalcemia is not a factor in the hypertension of pregnancy We²⁰ have reinvestigated the significance of the potassium-calcium ratio and the inorganic phosphorus, with the aid of recently devised exact methods, in 75 cases of hypertension and in 25 control cases The potassium and calcium content of the blood in patients with uncomplicated hypertension was normal In patients with cardiac complications the potassium content was somewhat high We were unable to find any correlation between the potassium-calcium ratio of the blood and hypertension Elevation of the ratio, when present, was the result of circulatory failure

Peptones Hulse and Strauss²⁹ of the Volhard Clinic have claimed that peptone-like substances in the blood of patients with hypertension caused by glomerulonephritis and eclampsia are responsible for hypertension, inasmuch as these circulating substances sensitize the effect of circulating epinephrine causing vasoconstriction This problem was again investigated at the Boston City Hospital by Jackson³⁰ who, after devising an accurate method for the determination of peptones in the blood, failed to observe any elevation in patients with hypertension

Epinephrine and Pituitrin While the aforementioned chemical theories are related to substances which can be determined chemically in the blood or the urine, the suggestion that circulating hormones, particularly epinephrine and pituitrin, are responsible for hypertension is supported by indirect evidence only. Ever since the discovery by Oliver and Schafer³¹ of the pressor effect of extracts of the medulla of the suprarenal gland, it has been suggested by Vaquez³² and other clinicians^{33, 34, 35, 36} that hyperadrenalemia is responsible for at least a certain type of hypertension. These suggestions, however, are not supported by the demonstration of an increased epinephrine content of the blood. While earlier investigators have claimed to demonstrate such an increase with biologic tests, their observations have remained unconfirmed even when such sensitive tests were applied as were claimed to give a positive reaction in a 1:700,000,000 dilution.³⁷ The comparative analysis of the adrenal gland for epinephrine also failed to yield convincing evidence that the epinephrine content of the gland from patients with hypertension differs from that in normal subjects.^{38, 39} Hence the only tangible evidence in favor of the epinephrine origin of hypertension is the apparent correlation between certain hyperplasias and tumors of the adrenal gland, and arterial hypertension. It should be remembered, however, that hyperplasia and adenoma of the cortex are frequently not associated with hypertension, but these frequent negative findings in postmortem examinations are not reported. Furthermore, no evidence exists that the cortical tissues of the adrenal gland contain vasoconstrictor substance. There are reported in the literature a few cases of tumors of the adrenal gland, partly of medullary and partly of cortical origin, which were associated with hypertension of severe and at times widely fluctuating course.^{40, 41, 42} Whether the cause of arterial hypertension in these rare instances was epinephrine, or whether the tumor and the hypertension were coincidental parts of a constitutional make-up, or, finally, whether the tumor induced certain changes in the bodily structure which then indirectly caused arterial hypertension, cannot be determined from the available evidence.

The *pituitary theory* as to the origin of certain types of hypertension has aroused much interest recently, mainly through the contributions of Anselmino^{43, 44} and Cushing^{45, 46, 47, 48}. Anselmino and Hoffmann have claimed to demonstrate that the blood and urine of women with eclampsia and arterial hypertension contain increased amounts of a substance which exerts a vasopressor and an anti-diuretic effect. These investigators have claimed that the substance is pituitrin. Recently, however, Hurwitz and Bullock⁴⁹ at the Boston Lying-In Hospital, and Page⁵⁰ at the Rockefeller Institute were unable to confirm the observations of Anselmino. In describing the syndrome of basophilic adenoma, Cushing⁴⁷ has called attention to the fact that arterial hypertension is frequently present. In support of his theory of the pituitary origin of hypertension he cites the work of Anselmino^{43, 44} and the observation of increased basophilic cells of the anterior lobe in the presence of hypertension.^{51, 52, 53} Since two groups of

investigators have failed to confirm the work of Anselmino, and since the significance of increased basophilic cells in general, and their presence in hypertension in particular, is not clear, Cushing's theory on the etiology of hypertension still lacks adequate evidence. In view of the association of basophilic adenoma with bodily changes involving different types of tissues, the interrelation between basophilic adenoma and hypertension is open to a number of other explanations than the effect of circulating pituitrin.

Increased *thyroid secretion* has also been held responsible for arterial hypertension,^{54, 55} but an examination of the data fails to reveal any direct relationship between hyperthyroidism and true arterial hypertension.

Vasoconstrictor Substances of Undetermined Nature If epinephrine, pituitrin or other substances with a vasoconstrictor effect are responsible for the development of arterial hypertension, obviously one would expect to be able to demonstrate an increased vasoconstrictor effect induced by concentrated extracts of the blood and urine. A series of such investigations has been conducted mainly by the Volhard school in recent years. Bohn and his associates^{56, 57, 58, 59} claim that extracts of the blood and urine of patients with the so-called "pale hypertension" of Volhard, which includes cases with glomerulonephritis, malignant hypertension and eclampsia, exert a marked constrictor effect on the vascular systems of rabbits and cats. Marx⁶⁰ has observed similar responses in unanesthetized dogs following the injection of extract of blood from a group of patients. Although we do not entirely agree with the rationale of Volhard's rigid classification of "pale" and "red" hypertension, nevertheless Capps, Ferris, Taylor and I⁶¹ have reinvestigated the problem of circulating vasopressor substances in the blood and particularly in the urine. We were able to demonstrate a pressor substance in the blood and in the urine in normal subjects, as well as in patients with hypertension. This vasopressor substance, however, has no relation to the degree or to the type of hypertension. In our studies, the most powerful vasopressor substances were extracted from the urine of normal subjects. It is interesting that the available evidence indicates that this *vasopressor substance* acts on the vasomotor centers and that its effect depends on the state of these centers. The work of Bohn and Marx has also been disproved recently by de Wesselow⁶² and Page.⁶³

Alcohol and Tobacco Among the exogenous chemical factors, alcohol and also tobacco have been held responsible for the development of hypertension. Without giving a detailed analysis of the literature⁶³ one may conclude that both pharmacologic and clinical evidence is lacking to support the claim that alcohol is responsible in any manner for arterial hypertension. Similarly, no convincing data are available on the etiologic influence of tobacco.⁶⁴ Although evidence is available indicating that tobacco and nicotine can induce elevation of the blood pressure in animals,^{65, 66} and that patients with arterial hypertension may exhibit accentuation of the elevation of the blood pressure during a period of excessive smoking, there are no data indicating that nicotine plays a rôle in the causation of hypertension.

The fact that a statistical analysis of the sex incidence in a large group of cases of essential hypertension at the Boston City Hospital⁶⁷ revealed a greater frequency among females may also be used as indirect evidence against the significance of alcohol and tobacco in hypertension.

Lead There is only fair evidence that lead is responsible in some instances for the development of arterial hypertension. Pharmacologic studies and clinical observation reveal clearly that lead compounds exert a constrictor effect on smooth muscles^{68, 69}. Temporary hypertension in acute poisoning, particularly during lead encephalopathy, is frequently observed. That patients who suffer from chronic lead poisoning exhibit an increased incidence of sclerosis of the arterial vessels and elevation of the blood pressure is also suggestive. The development of this true, persistent hypertension is due to a sclerosis of the vascular system^{70, 71, 72}. Obviously, however, lead explains but a small fraction of the cases of hypertension.

Thus, to summarize the results of investigators of more than two decades, while a priori the theory of the etiologic rôle of circulating vasoconstrictor substances seems plausible, actually extensive experimental and clinical studies fail to support such a contention. Lead is probably responsible for a few instances of hypertension. The correlation between certain tumors of the adrenal and pituitary glands and hypertension is suggestive, but the nature of this correlation is not known. Constitutional rather than direct hypersecretory functions are probably active. While this negative conclusion may appear to be discouraging, actually it is constructive for it allows us now to turn our attention more definitely toward other possibilities.

2 THE RÔLE OF THE NERVOUS SYSTEM IN THE CAUSATION OF HYPERTENSION

The significant rôle of the nervous mechanism in the regulation of blood pressure is well known. Although recent years have seen important progress in the field of the chemical regulation of the circulation, as well as in the field of neurochemical interrelations, today the dominant rôle of the nervous system in the regulation of blood pressure stands out even more definitely. In this nervous regulation, the sympathetic vasomotor system with its constrictor influence is a primary factor, its effect being partially inhibited by the parasympathetic vasomotor nervous system, particularly through the carotid sinus and the aortic depressor reflexes^{73, 74, 75}. The regulation of the blood pressure results through a shift of the sympathetic-parasympathetic vasomotor nervous balance owing either to decreased function of the depressor (parasympathetic) reflexes, or to increased activity of the pressor (sympathetic) reflexes. That experimental elimination of the depressor reflexes actually induces arterial hypertension has been demonstrated recently^{74, 76}.

It has been suggested, therefore, that *hypoactivity of the carotid sinus and other depressor reflexes* is responsible for arterial hypertension.

suggestion, however, based on animal experimentation, is not supported by clinical studies. If hypoactivity of the carotid sinus reflex is responsible for the development of arterial hypertension, one would expect the depressor response to be reduced or absent following stimulation of the sinus. Such is not the case in our experience, for mechanical stimulation of the sinus of patients with hypertension resulted in a relatively increased rather than in a decreased depressor response.⁷⁷ It may be contended, however, that although mechanical stimulation of the carotid sinus induces a hyperactive response under physiologic conditions, atheromatous changes in the sinuses and in the aorta may interfere with transmission of the intravascular pressure to the sensory nerve endings. Under such conditions the nerve endings may continue to respond to direct external mechanical stimulation, and yet intrasinal pressure changes would result in but slight or no reflex response. Such a suggestion of Hering⁷³ can be rejected on the basis of the careful histologic studies of Sunder-Plassmann,⁷⁸ who observed a lack of correlation between atheromatous changes in the sinus and degeneration of the nerve endings. Von Hasselbach,⁷⁹ and recently Keele,⁸⁰ found no correlation between the degree of structural change in the sinus and the aorta and the blood pressure level. In a clinical examination of the structural characteristics of the sinuses we have had similar results.^{77, 81} One may therefore conclude that studies on man do not favor the contention that hypo-function of the carotid sinus or aortic depressor reflexes is responsible for arterial hypertension. One should realize, on the other hand, that the rôle of decreased depressor reflexes requires further study.

The second possibility, namely, that an *increased pressor nervous mechanism* is responsible for arterial hypertension, is based on fair evidence. The fact that a constriction of the arteriolar system exists in hypertension is generally accepted.^{82, 83, 84} This narrowing of the arteriolar system is present in hypertension of different types, although the extent and the organ distribution may vary in the same as well as in different types of hypertension. If narrowing of the arteriolar system results from constriction of the smooth muscles, it is obviously due to increased tonus of the sympathetic system. The sympathetic system is the constrictor and the dominant portion of the vasomotor nervous system, hence variations in its tonus are to be expected. From a comparative study of a group of patients with essential hypertension and a control group, we⁸⁵ have concluded that, on the whole, the influence of the sympathetic nervous system was more pronounced and that of the parasympathetic less so in patients with hypertension than in control subjects with normal cardiovascular systems. This increased sympathetic balance was a statistical conclusion and was not present in every case. The question now arises as to the cause of this increased tonus of the sympathetic nervous system. To state, as von Monakow⁸⁶ has done, that the vasomotor center is "set" on a higher level in hypertension, is not particularly constructive in the further analysis of the problem. Bordley and Baker⁸⁷ have claimed that ischemia resulting from arteriosclerosis of the medullary

centers is a factor. Cutler's ⁸⁸ more recent study, as well as routine experiences, throws much doubt on the general rôle of medullary arteriosclerosis. That this factor, as well as local circulatory disturbances from pressure caused by tumors or other intracranial pathology, may play a rôle in some instances, seems very plausible. Studying the cerebral circulation of patients with essential hypertension, Raab ⁸⁹ in our laboratory has observed an increased oxygen difference indicating a slower blood flow through the brain. He has interpreted this finding as indicating ischemia of the cerebral circulation in hypertension. In view of the ages of the patients studied, as well as of the presence of arteriosclerosis, and because our later experience has demonstrated a more severe degree of cerebral ischemia in a number of conditions unassociated with hypertension, we cannot agree with Raab's conclusions. The ischemic etiology of the hypertonus of the vasomotor center cannot be accepted at present as the cause of hypertension.

Because patients with essential hypertension often exhibit an accentuation of the elevation of the blood pressure under *emotional stress*, and a fall during relaxation, the emotional etiology of hypertension has also received much attention. On careful examination, however, this theory does not seem to be so obvious as on first inspection. Dramatic examples of elevation of the blood pressure under stress and its fall to normal during relaxation are not lacking. Statements that patients with hypertension present a high-strung, driving personality and that hypertension is a condition of our modern age of wear and tear are also numerous in the literature ^{90, 91}. Whether vascular diseases with arterial hypertension are really modern diseases is quite doubtful. Apoplexy, heart failure of nonvalvular origin, and uremia have always been common clinical manifestations. Hypertension occurs frequently among the population of quiet, farming villages. The rôle of emotions in hypertension is not so evident in hyposensitive races as in hypersensitive and rather excitable races. Careful analytical study of the psychic make-up of hypertensive patients, including control observations, is still lacking. The difficulty of the problem is further increased by the fact that frequently during elevation of the blood pressure, changes in personality appear which are secondary to the elevation of the blood pressure ⁹². In a comparative analysis of a group of patients with essential hypertension and with normal cardiovascular systems, overexcitability, impulsiveness and a tendency to worry was, nevertheless, more frequently present in the hypertensive group ⁸⁵. In a study of 1090 ambulatory patients with essential hypertension, we ⁹³ have observed a symptomatology quite similar to that in patients with neurosis. This was also found by Davis ⁹⁴ and by Ayman and Pratt ⁹⁵. We ⁹³ have pointed out, however, that a large control group of patients with obesity and with psychoneurosis, but with normal blood pressure, exhibited the same symptomatology as patients with arterial hypertension. Thus, although psychic trauma and conflicts, as well as abnormal sensitivity of the psyche, play a rôle in essential hypertension, personality and emotional factors *alone* are not adequate in the

explanation of even a single type of hypertension. This contention is also supported by the fact that emotional disturbances in psychoses bear no relationship to the level of the blood pressure. It has been rightly emphasized by Dennig, Fischer and Beisinger⁸⁶ that no close relationship exists between "cortical" and "autonomic" functions. If, on the other hand, in hypertension a closer interrelation exists between the psychic factor and the sympathetic centers, this requires further explanation.

In addition to the suggestive central origin of essential hypertension, it is possible that pressor reflexes play an important rôle in hypertension associated with primary genito-urinary pathology.

3 THE REACTIVITY OF THE VASCULAR SYSTEM AND MECHANICAL FACTORS

As has been pointed out, an increased resistance of the arteriolar bed caused by a narrowed arteriolar system is one of the main features of the bodily state in hypertension. Such a generalized change in the arteriolar resistance is satisfactory explanation for the development of the majority of types of hypertension. One mechanism in the development of a narrowed arteriolar system, namely, increased nervous tonus, has already been discussed. A second possibility, namely, a primary cellular or mechanical origin, also merits careful consideration.

An increased constrictor response of the minute vessels to local heat and mechanical stimuli has been observed in patients with essential hypertension both by Lange⁸⁷ and in our laboratory⁸⁸. Although we do not at present possess data on the total transectional area of the arteriolar system, clinical and postmortem experiences reveal variations in the arterial lumen in different subjects. At times the narrowed state of the vascular system of women in good health, who later develop hypertension during pregnancy, is striking. It is also established that with advancing age there is progressive accumulation of intercellular cement substances, loss of elasticity of tissues, arteriosclerotic and other involutionary changes which are all included in the collective term of "changes of senescence". These changes result in the shrinkage of the lumen of the small arterial vessels and in a secondary progressive rise in blood pressure. A moderate degree of progressive rise is thus an expression of physiologic senescence. In persons with congenitally hypoplastic arterial systems, however, the normal changes of senescence result in a marked increase in the vascular resistance. In persons with increased severity of degenerative changes an increased arteriolar resistance also develops. That mechanical factors of increased peripheral resistance play a role in arterial hypertension is demonstrated by cases of coarctation of the aorta, in which elevation of the blood pressure exists in vascular areas originating from portions of the aorta in front of the resistance, and by cases of obesity in which the hypertension may completely disappear with reduction of body weight. The fact that a sudden rise in

the incidence of hypertension coincides with the age of onset of involutionary changes of the body in each sex, also supports this view⁶⁷ Thus in a study of the age distribution of 1620 ambulatory patients with hypertension, the bulk of the cases were noted after the age of 40, coinciding with the onset of involutionary changes, such as climacteric, and not in youth when the sensitivity of the nervous system is greatest and when mild, temporary emotional hypertension is relatively common^{68, 69} The finer mechanism through which a primary generalized increased arteriolar resistance of nervous, cellular or other origin results in an increased cardiac force and hence in hypertension, is not clear It has been suggested that with the increased arteriolar resistance as the result of local ischemia, tissue metabolites stimulate efferent nerve endings of a widespread cardiopressor reflex¹⁰⁰

It has also been claimed recently that in certain types of essential hypertension, in addition to changes in the minute vessels there is a progressive loss of elasticity and of the propulsive action of the aorta and other large vessels^{101, 102, 103} The decreased elasticity of these large arteries also explains the relatively high systolic pressure and the high pulse pressure without increased cardiac output which were observed by us recently⁸¹ This pertinent problem, particularly as to whether changes in the arteries occur early or only in the later stage, merits further investigation

The mechanical theory that hypertension of nephritis is due to local vascular resistance of the kidneys, first proposed by Traube,¹⁰⁴ is not tenable, both because of theoretical objections and because our studies of the hemodynamics of the circulation in hypertension of nephritic origin reveal a widespread vasoconstriction⁸³ That local disturbance of the renal circulation can induce experimental hypertension, on the other hand, has been shown repeatedly Such an experimental hypertension has been induced by excising varying amounts of kidney tissue,^{105, 106, 107, 108, 109} by damaging the kidney with roentgen-rays,¹¹⁰ by local renal venous stasis,^{111, 112, 113} and recently by progressive clamping of the renal arteries¹¹⁴ Fahr¹¹⁵ maintains that renal ischemia plays a rôle in the induction of hypertension associated with nephrosclerosis There are, indeed, a number of clinical examples indicating that local diseases of the genito-urinary tract are followed by arterial hypertension The explanation of hypertension of kidney and genito-urinary system origin does not lie in increased local vascular resistance but, as has been pointed out recently by Goldblatt, Lynch, Hanzal and Summerville,¹¹⁴ is based on one or more of the following possibilities (a) afferent impulses are set up from the affected nerve endings in the ischemic kidneys to the vasomotor centers, whence a general vasoconstriction is induced, (b) afferent impulses from the ischemic kidney may influence some internal secretory gland, and (c) there may be an accumulation or new formation of some substance or substances which, after entering the blood stream, induce a general vasoconstriction At present the exact mechanism of hypertension induced from the kidney and urinary passages is not known

4 THE RÔLE OF INFECTIONS AND VASCULAR ALLERGY

Evidence that infections play a direct etiologic rôle in the *majority* of instances of hypertension is lacking. Clinical observations, on the other hand, furnish ample evidence indicating an indirect etiologic rôle for infections. There is not a single type of infectious agent which is regularly associated with hypertension. The majority of infections associated with hypertension first produce kidney lesions, and hypertension then develops as a secondary manifestation. In this sense, streptococci are indirectly responsible for certain cases of hypertension. Similarly, urinary infections of childhood with pyelonephritis, or with partial stricture of the ureter, cause hypertension, which at times imitates the clinical picture of essential hypertension. The hypertension of mitral stenosis¹¹⁶ also represents such an indirect relationship. The apparent relationship between syphilitic aortitis and hypertension¹¹⁷ can be explained by changes in the aorta and particularly by narrowing of the lumen of arterial openings.

The claim that allergy plays a role in arterial hypertension^{118, 119} cannot be accepted as yet. In certain cases of malignant hypertension, particularly in periarteritis nodosa, infections such as peridental abscess, pyelitis, perinephritic abscess, seem to play an indirect rôle. The problem of vascular allergy has not been investigated with the care it deserves.

5 CONSTITUTION AND ARTERIAL HYPERTENSION

In the foregoing discussion we have concluded that vascular changes of senescence, local irritability of the vascular tissues, psychic factors, increased tonus of the autonomic nervous system, increased pressor reflexes, infections and lead play a rôle in the development of various types of arterial hypertension. It should be emphasized, however, that any of these factors may be present in even greater intensity in persons with normal blood pressure. Thus, although the rôle of the above factors stands out clearly, their relation to hypertension is not a direct and consistent one. The postulation, therefore, of an added factor seems inevitable. One may state with justification that these etiologic agents result in hypertension only if they act on persons with a certain psychophysical make-up. The fact that extensive investigations have failed to reveal any single factor which regularly causes arterial hypertension, strengthens the importance of the rôle of the constitution.

Detailed knowledge of this constitution is still lacking. It is probable that the physical aspect of the body habitus is the least important. Weitz,^{120, 121} de Nador-Nikitits¹²² and others deny that the sthenic habitus (megalosplanchnic habitus of Viola or pyknic of Kretschmer) has a special relation to hypertension. Daily clinical experience, also, suggests that among patients with pronounced hypertension all types of bodily habitus occur with approximately the same frequency. It is suggestive, then, that an understanding of the inherited anatomic and functional characteristics of the nervous and

vascular systems rather than the bodily habitus will eventually bring the solution. It is known that the vascular and nervous systems are particularly apt to transmit constitutional stigmata. Striking examples of a hereditary history in hypertension, nephritis, and cerebral vascular accidents have been known to clinicians ever since Forestus in the sixteenth century called attention to the hereditary occurrence of apoplexy.

O'Hare, Walker and Vickers¹²⁴ elicited a family history of vascular disease in 68 per cent of a group of patients with arterial hypertension. On the basis of an extensive study Weitz^{120, 121} concluded that hypertension is inherited as a dominant characteristic. Recently Ayman¹²⁵ has presented additional data on the rôle of heredity. The fact that a hereditary history cannot be obtained in a higher percentage of cases is natural, and does not invalidate the significant rôle of the constitution, for a hereditary history is but partial and rather crude evidence of hereditary constitution, and just as the dividing line between what constitutes a normal person and one with hypertension is ill-defined, so is there no hard and fast division between the constitutional characteristics possessed by the two types.

COMMENT

In a consideration of the pathogenesis of hypertension, the general nature of the problem must be viewed as a whole. Just as before the discovery of insulin it was of aid in research to consider diabetes mellitus as a disease caused by disturbed function of the islands of Langerhans, and hence primarily a deficiency disease, so it is equally important to appreciate that arterial hypertension is not a disease entity but a bodily state of multiple etiology. We use the term "arterial hypertension" only because we can measure conveniently an important aspect of the circulation. The alteration in the blood pressure, however, is not the primary, nor even the most important, aspect of the problem. Change in the minute arterial vessels, which we cannot measure at present, is the primary site of the vascular change. Not only is the character of these vascular changes varied, but the same type of change, such as diffuse arteriolar spasm, is induced by different etiologic factors.

In taking the level of the blood pressure as an index of peripheral vascular changes, we have selected a circulatory function which undergoes considerable variation even in health, for in the homeostasis of the body arterial tension is not a rigid constant, when compared with body temperature and chemical regulation of the blood. Hence, we are quite arbitrary in considering a systolic pressure of 145 mm Hg "normal" and a pressure of 155 "hypertension." The transition from a normal to hypertensive state is very gradual. In the majority of instances of hypertension we are dealing with but a moderate accentuation of the physiologic factors. Experience, on the other hand, has taught us that patients with markedly

elevated blood pressure frequently exhibit functional and structural disturbances of various organs, hence the clinical emphasis on the problem of hypertension is justified

In spite of numerous investigations with negative results and faulty conclusions, the labor of the past two decades has resulted in remarkable progress in this important and difficult field. The fact that we have put suggestions and theories to the acid test of experimental research in itself represents a great advance. Much is known today of the hemodynamics and the vascular state in arterial hypertension. We have appreciably clarified the reversible interrelation between hypertension and kidney pathology. We have also definitely ruled out the suggestion that alterations in the cardiac output, stroke volume, blood volume, or viscosity of the blood are primary factors in the pathogenesis of the disease. On having established the significance of the stenotic state of the arteriolar system and of diminished elasticity of the larger arteries, today we are permitted to turn our efforts toward the primary etiologic mechanisms. Much is yet to be learned concerning this aspect of the problem. The fact, however, that extensive and painstaking search has failed to reveal any single factor of chemical or nervous nature which specifically and regularly induces hypertension seems to us very significant. It suggests that we may be dealing with a condition of multiple rather than of single etiology. Perhaps success in unfolding the nature of diseases of primary or of single etiology has wrongly trained us in the past half century to search always for a single cause of a disease.

From the above presentation it is clear that a number of factors definitely bear on the etiology of hypertension. It was emphasized that the factor or factors which are definitely active in a given case may not be present in all cases of the same type of hypertension, and furthermore the factors responsible in hypertension may occur in subjects with normal blood pressure. We wish to emphasize that this apparent contradiction does not obviate the rôle of these factors, but it suggests a special "affinity" or "susceptibility" on the part of the patient for these precipitating factors. Physiologic examples in human beings are numerous showing that an identical nervous or chemical stimulus exerts its effect on different organs in different groups of subjects.¹²⁶ Thus in the study of the etiology of arterial hypertension we should always analyze the primary constitutional characteristics of the patient, as well as the secondary precipitating factors. Today suggestive experimental and clinical evidence is available indicating that the role of inheritance and constitutional predisposition are represented mainly by inherited and at times acquired local irritability of the minute vessels, hyperirritability of the sympathetic vasomotor centers, and hypoplastic development of the vascular system. Among the secondary factors acting on such constitutionally susceptible nervous and vascular systems are emotional stress, physiologic changes of involution and senescence, obesity, certain types of infections, reflexes, particularly from the genito-urinary organs, and a few exogenous chemical substances. The relative rôle of

these factors varies considerably. The present evidence indicates that in the great majority of instances involutionary and senescent changes are active in the constitutionally predisposed individuals. The present classification of primary or essential (benign and malignant) and secondary hypertension of kidney origin indicates mainly the clinical and morphologic state of the body, but does not correspond to a single characteristic etiology.

The interpretation of hypertension as given here carries with it a certain amount of argument against the possible effectiveness of drugs, serologic or substitutional therapy. It implies that prevention and elimination of the secondary precipitating factors represent the main approach in treatment. While such a belief may seem pessimistic, since it eliminates at once the rationale of a search for a "cure," it is, nevertheless, in accordance with clinical experience, and furthermore emphasizes the rôle of physicians as advisors of patients rather than as dispensers of medication.

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INFLUENTIAL FACTORS IN RECOVERY FROM RHEUMATOID ARTHRITIS^{*}

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EVERY physician knows that there is more than one factor which enters into recovery from an infectious disease. These various factors are constitutional or environmental. It occurred to me that it might be interesting to consider at this time the more important factors which influence recovery in one of our commoner infections, namely rheumatoid arthritis. At the outset some may object to the assumption that rheumatoid arthritis is a chronic infection. It must be admitted that the evidence for its infectious nature is not complete, but the fact remains that the majority of investigators in this field now consider it a chronic infection, and the writer will therefore discuss the disease from the infectious point of view in the present paper.

Any kind of discussion of rheumatoid arthritis is always handicapped by the fact that we know so little concerning the origin and nature of the disease. In observing a patient with rheumatoid arthritis we see pathologic changes and symptoms which bear all the earmarks of a chronic infection. But just *why* the patient develops the disease, or exactly *how* he develops it are still subjects for speculation. This, of course, is true of other infections which are better understood than rheumatoid arthritis. "First causes" in medicine are always problematical. Let us, therefore, concern ourselves no longer with the teleology of this disease, but proceed at once to a discussion of the factors which influence, or appear to influence, recovery from it.

CONSTITUTION

We can do no better than begin with constitution. Is there such a thing as a constitutional diathesis toward rheumatoid arthritis? The writer believes that there is. I have seen too many long lanky men and women with the disease to question the tendency of this type toward rheumatoid infection. This of course is the so-called tuberculous type and raises the question whether there is any basis for the contention now being made by certain German writers that rheumatoid arthritis is a form of tuberculosis. One sees stocky, and even obese, patients in an arthritis clinic, but most of them are suffering from hypertrophic rather than from rheumatoid arthritis, and many of the rheumatoid patients who appear rotund have been slender and long-trunked in their younger days. I would not deny, of course, that the stocky, so-called brachycephalic type can develop rheumatoid arthritis, but I think it is an exception to the rule, and I am quite sure that the stocky type responds more readily to treatment than do the dolichocephalics.

^{*} Read at the Chicago meeting of the American College of Physicians, April 19, 1934.

TEMPERAMENT

Closely allied to constitution is the question of temperament. Neurotic, introspective patients are more difficult to relieve than buoyant cheerful ones. The natural melancholy of the Jewish race has always seemed to me a distinct handicap to their recovery from rheumatoid arthritis, though here again there are many exceptions. I have often wondered why so many spinsters develop the rheumatoid syndrome. I doubt if the sex hormones are influential in this connection. It appears more likely that the really predisposing factor is the temperament of the patient.

HEREDITY

There is great need for a thorough-going, scientific study of heredity in relation to rheumatoid arthritis. There are very few articles on this subject in medical literature. Marinesco and Allende¹ have recently reported the cases of two brothers and a sister, all of whom developed in the early years of their childhood the deforming type of chronic infectious arthritis, so-called Still's disease. The writer recalls from his own experience two families in which the incidence of rheumatoid arthritis was amazingly high. In one of these families the disease could be accurately traced through four generations (Table 1). Such extreme examples are unusual, but the hereditary factor may be more important than we have realized. Certainly a great many of the writer's patients testify that one or both of their parents suffered from chronic arthritis. The difficulty arises in determining what type of arthritis the parent had—that is, whether it was rheumatoid or hypertrophic in character. Some of our young students of arthritis could hardly find a more interesting problem for investigation than the rôle of heredity in rheumatoid arthritis. I should add that in those cases where heredity appears to play an important part, the patient often progresses to the deforming and ankylosing stage of the disease in spite of all treatment.

RACE

So far as the writer knows, no race is immune to rheumatoid arthritis. I suspect that the dark races are less susceptible than the white races, but this may be due to differences of habits or environment rather than to any variations in racial immunity.

AGE

Rheumatoid arthritis may develop at any age and may be a formidable menace to health at any age. Cecil and Archer² found the highest incidence of onset was at 35. So far as recovery is concerned, I used to think that young adults offered a better prognosis than patients who developed the syndrome late in life. With increasing experience, however, I am not so

thoroughly convinced on this point I have recently seen several patients who developed rheumatoid arthritis after 60, and who have responded promptly to treatment Tuberculosis is supposed to deal more kindly with the middle-aged and elderly than with young adults, and the same may be true of rheumatoid arthritis This point can be settled only by careful statistical studies Middle-aged and elderly patients are more cooperative than young people and follow the physician's instructions more carefully On the other hand, they often have to contend with a coexisting osteoarthritis, which may set up a sort of vicious circle in the joints affected

SEX

I am sorry to say that I have no figures on the incidence of recovery from rheumatoid arthritis with respect to sex We do know that women are two or three times as susceptible to the disease as are men, and my impression is that in general men respond more quickly to treatment than do women

CLIMATE

The final chapter on the relation of climate to the incidence of rheumatoid arthritis and to recovery from this disease has yet to be written It is claimed, and I suspect rightly, that the natives of Arizona and New Mexico never develop rheumatoid arthritis It is rarely seen in the tropics, though I believe it is fairly common in some of our southern cities, such as New Orleans Certainly it is commoner in the southern part of the United States than rheumatic fever We have yet to determine, however, just how much better the prognosis of the rheumatoid patient is in Arizona than it is in the eastern part of the United States, assuming that the other environmental factors are the same What I mean to say is this How much higher is the percentage of recovery for arthritic patients in an Arizona sanatorium than it would be for patients in a New York or Pennsylvania sanatorium? This question can be answered only by carefully prepared statistical and follow-up studies Theoretically Arizona, because of its wonderful climate, should have the best of it, but unfortunately even Arizona fails with many of our more stubborn cases

ECONOMIC STATUS

Rheumatoid arthritis is like tuberculosis and rheumatic fever It is more prevalent among the poor than among the well-to-do, and the former do not respond so well to treatment The poor are more exposed to cold and damp weather, their food is not so well cooked, their diet often poorly balanced They have not the means of getting proper medical attention, and more important still, they have not the time or money for rest cures

JOINTS INVOLVED

The outcome in rheumatoid arthritis depends to some extent on the joints involved. When the fingers are first attacked it often seems to confer some immunity against involvement of the larger joints. The knees are bad joints mechanically and always present a difficult problem, not only because of the intricacy and size of the joint, but because it is a weight-bearing joint. I have often noticed that in convalescent patients the knees and feet will be the last to recover, usually because the patient becomes restless, discontinues rest and starts walking before the joints have healed completely. The hip is usually one of the last joints to be affected in rheumatoid arthritis, and this is indeed fortunate, because infection of the hip joint is painful and yields very slowly to treatment.

Perhaps the most stubborn of all is the infectious spondylitis of the Marie-Strumpell type. "Poker spine" is a hard disease to check. It occurs almost exclusively in young males and often runs a rapidly progressive course, producing marked rigidity of the spine and ankylosis of the shoulders and hips.

EFFECT OF OTHER DISEASES ON DEVELOPMENT AND COURSE OF RHEUMATOID ARTHRITIS

I have recently become interested in investigating the effect of other diseases on the incidence and course of rheumatoid arthritis.

Focal Infection I suppose no one would deny the importance of focal infection in the etiology and course of rheumatoid arthritis. The fact that the removal of foci of infection does not always lead to recovery from arthritis detracts in no way from its significance. A great many people carry foci of infection for years without any joint symptoms. A certain number will develop arthritis. Why some get the disease and others escape, we do not know, but we cannot avoid the conclusion that focal infection is an important predisposing factor in the etiology of rheumatoid arthritis and that the elimination of such foci is a fundamental step on the road to recovery.

Pulmonary Tuberculosis Rheumatoid arthritis is comparatively rare in tuberculous patients. Pemberton³ is my authority for this statement, which is in agreement with my own personal experience. The two diseases do occur, however, in the same patient as the following example will show.

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Pulmonary Tuberculosis

R H Female Aged 26

| | |
|------|--|
| July | 1930—Migratory progressive pain and swelling of joints |
| Nov | 1930—Hemorrhage Diagnosis Pulmonary tuberculosis |

- Summer, 1931—Saranac "Extensive pulmonary tuberculosis" Pain and swelling of joints
- 1932 to 1933—At Saranac Marked improvement in both conditions Became practically free of symptoms
- May 1933—Return of pain and swelling of joints
Rales at left apex
Agglutination *Streptococcus hemolyticus* 1 320 Sedimentation rate 13 WBC 8,000 Tonsils out Vaccine, etc
- March 1934—No signs of tuberculosis Practically free of joint symptoms

The arthritis in this case never presented the picture of a tuberculous infection Furthermore the agglutinins for *Streptococcus hemolyticus* in the patient's serum identified the disease as rheumatoid arthritis

Syphilis When chronic arthritis develops in a syphilitic patient, one must be sure that he is not dealing with a syphilitic arthritis This differentiation, however, is usually easy as luetic arthritis, like tuberculous arthritis, usually involves only one joint The following case presented all the symptoms and signs of rheumatoid arthritis and occurred in a patient with a strongly positive Wassermann

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Syphilis

G D Female Aged 44

1925—Onset of rheumatoid arthritis

April 1930—First seen by writer Mild rheumatoid arthritis Chronic sinusitis
Several fusiform fingers Agglutination *Streptococcus hemolyticus*
1 1280

April 1931—No improvement after one year of routine treatment
Wassermann 4 plus (controlled)
Husband 4 plus
Salvarsan and bismuth

Oct 1931—Rapid disappearance of all arthritic symptoms

The improvement in the arthritis was so marked after the introduction of specific therapy that one might have suspected this of being a luetic arthritis but for the high agglutination with *Streptococcus hemolyticus* The chronic focus in the sinus and the typical fusiform fingers also supported the diagnosis of rheumatoid arthritis It seems fair to assume that in this case rheumatoid arthritis developed in a patient whose resistance had been lowered by a previous luetic infection and that when the latter was brought under control by specific therapy, the patient soon got control also of the arthritic condition We might also suspect that in this case the arsenic in the salvarsan was of distinct benefit to the arthritic as well as to the syphilitic infection

Rheumatic Fever It would not be appropriate in this discussion to take up the relationship of rheumatic fever to rheumatoid arthritis This question has recently been discussed at length by Dawson,⁴ who believes that the two diseases are very similar in character We do know that a few

cases of rheumatic fever progress into a condition indistinguishable from rheumatoid arthritis I can recall one young man in my own practice who, subsequent to rheumatic fever, developed rheumatoid arthritis and, after suffering with it for two or three years, finally made a complete recovery His only residual lesion was a severe mitral endocarditis

Gout The etiology of gout is still a subject of much debate Some writers speak of it as a metabolic disease Others consider it an allergic condition, and still others an infection The writer is quite sure that on more than one occasion he has encountered rheumatoid arthritis and gout in the same patient The following two cases will serve as good examples

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Gout

J W Male Aged 39

- 1913—Acute gout in great toe
 1913 to 1928—Sporadic attacks in right great toe Becoming more frequent
 1928 to 1932—Attacks of polyarthritis
 June 23, 1932—First seen by writer Chronic podagra Arthritis of ankles and knuckles Fusiform joint, left ring finger Uric acid 6.5 mg
 Agglutination *Streptococcus hemolyticus* 1:2560
Streptococcus hemolyticus 3 plus positive in throat culture
 July 26, 1933—Much improved after a year of treatment Agglutination *Streptococcus hemolyticus* neg Uric acid 4.3 mg
 1933 to 1934—Occasional attacks of gout, but arthritis no longer active

This patient undoubtedly had gout, and the high agglutination with the *Streptococcus hemolyticus* pointed strongly toward a concomitant rheumatoid arthritis The swelling and pain in various joints and the fusiform ring finger were also strongly indicative of rheumatoid arthritis

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Gout

R S R Male Aged 51

- July 1931—Progressive polyarthritis with swelling, fusiform fingers, etc
 Jan 1932—First seen by writer Typical rheumatoid arthritis Agglutination *Streptococcus hemolyticus* neg Sedimentation rate 12 mm Uric acid 4.2 mg
 April 1933—Arthritis much improved Fusiform fingers almost disappeared Sedimentation rate 15 mm
 Sept 1933—Arthritis much improved, but patient has developed typical gouty bursitis on both elbows Colchicum, atophan, etc Uric acid 5.1 mg
 Jan 1934—Feeling fine, gaining weight "Bags" on elbows much smaller Sedimentation rate 0.8 mm Uric acid 3.7 mg
 April 1934—Relapse Pain and swelling in toes, elbows and right hip Sedimentation rate 16 mm Uric acid 5.0 mg

This patient is still under observation He is slowly recovering from

a severe joint condition, one which I and others thought would surely result in permanent crippling

Pernicious Anemia The writer has no very definite impressions concerning the effect of a coincident pernicious anemia on the course of rheumatoid arthritis. An appeal to my friend, Dr George Minot,⁵ brought the following interesting reply, which I have his permission to quote

The patient was a woman of about 60 years of age with typical pernicious anemia, whom I had suspected of having pernicious anemia several years before treatment was begun. Typical rheumatoid arthritis had existed for at least five years in a mild form. Under treatment with liver extract, the blood picture returned to normal. About the time the blood became normal, there was a sharp exacerbation in the rheumatoid arthritis. During the period of improvement her appetite was vastly better than it had been for many years, and she gained a moderate amount of weight. For the flare-up in her arthritis a rest program and a diet containing fewer calories were prescribed. After approximately six months the rheumatoid arthritis had lost its intensity and she was definitely better. At a later date this patient gave up liver, of her own accord, and relapsed. The arthritis remained quiescent, but increased in intensity as she got better again. This all happened over four years ago. I saw her about four months ago and she has remained in good health.

On the contrary, there are other cases I can cite where practically the reverse state of affairs took place. One was a female 40 years old. Arthritis in this instance was the presenting symptomatology of long duration, certainly five years. The anemia developed slowly, at first it was thought to be hypochromic, examination, however, showed it to be macrocytic. Tongue symptoms appeared. Increased rheumatoid arthritis was obvious at the time the blood was low (approximately two million red cells per cu mm) and in this instance, coincident with return of the blood to normal, the arthritis improved pronouncedly. In this latter case the individual was definitely under-weight, in the former case the patient was a little over-weight, even during the relapse in pernicious anemia.

Dr Minot feels as I do, that without many more case studies, we can say nothing definite about the relation between these two diseases.

Psoriasis The frequent coexistence of psoriasis and rheumatoid arthritis has long been a subject for comment. The writer has the impression (which, however, is not based on statistics) that few if any of the arthritics with psoriasis ever make a complete and permanent cure of either disease, though they may improve under treatment. In the German and French literature this syndrome is spoken of as *arthritis psoriatica*. Bauer and Vogl⁶ showed that in certain families, some members were suffering from psoriasis only, some from a polyarthritis only, while some presented the combined syndrome. They further claim that different types of joint diseases are to be met with in patients suffering from psoriasis, though they admit that the arthritis is usually of the chronic infectious or rheumatoid type. In one family Bauer and Vogl encountered an intermittent hydrops in association with psoriasis. Several other members of the family also had psoriasis and one of these suffered in addition from rheumatoid arthritis.

The following two synopses are taken from my own case records

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Psoriasis

J M Female Aged 25 Psoriasis since age of 7

| | |
|-------|--|
| | 1918—Gradual onset of rheumatoid arthritis |
| Oct | 1927—Severe rheumatoid arthritis Psoriasis all over body |
| Nov | 1927—Tonsillectomy, streptococcus vaccine, etc |
| Jan | 1928—Joints improving Psoriasis better |
| Sept | 1928—Recurrence of arthritis Return of psoriasis |
| Jan | 1929—Feeling fine Slight improvement in psoriasis |
| April | 1929—Some pain in joints Increase in psoriasis |
| Dec | 1929—Return of symptoms in joints and more psoriasis |
| Dec | 1930—Pain in back and joints Psoriasis troublesome |
| Jan | 1931—Joints comfortable Much less psoriasis |
| March | 1934—Arthritis much improved Psoriasis persists |

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Psoriasis

A T Male Aged 47

| | |
|--------------|--|
| | 1915—Gradual development of rheumatoid arthritis Psoriasis appeared about same time |
| 1924 to 1926 | —Almost free of symptoms "Psoriasis always better when joints are better" |
| | 1927—Return of arthritis |
| Jan | 1931—First seen by writer Extensive rheumatoid arthritis Spots of psoriasis all over body Streptococcus vaccine intravenously, diet, etc |
| March | 1931—Much improved Psoriasis fading Scales disappearing |
| April | 1931—Steady improvement in joints and in psoriasis |
| Sept | 1931—Practically free of symptoms Psoriasis almost gone |

These two case histories illustrate a fact that I have long recognized, namely that arthritis and psoriasis improve or regress together I have seen a good many patients with rheumatoid arthritis and psoriasis, and I feel moderately certain that when one condition improves, the other improves

Hyperthyroidism A good deal has been written about the relation of arthritis to the thyroid gland, but there is no convincing proof of any connection between the two The following case, however, has certain points of interest

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Hyperthyroidism

W J Male Aged 29

| | |
|------|---|
| May | 1929—Onset of rheumatoid arthritis |
| Jan | 1930—Sinus operation Rest in hospital 2 months Florida 2 months |
| June | 1930—Returned to work |
| Aug | 1930—Relapse |
| Oct | 1930—First seen by writer Severe rheumatoid arthritis and spondylitis Agglutination <i>Streptococcus hemolyticus</i> 1 160, |

Nov 1930—Tucson
 Dec 1930—B M plus 35 (controlled) Weight 92 lbs
 Feb 1931—Thyroidectomy
 Dec 1931—Remarkable and complete recovery except for some residual stiffness in spine

The improvement in this patient's condition following thyroidectomy was quite remarkable. One would expect a priori that a high basal metabolism would react favorably in a patient with rheumatoid arthritis. Indeed, thyroid extract has been recommended by more than one authority as a valuable agent in the treatment of rheumatoid arthritis. In this particular case, however, the arthritis progressed unfavorably in spite of all treatment until the metabolism was brought back to normal by thyroidectomy.

Diabetes Diabetes is a much commoner associate of hypertrophic arthritis than it is of the rheumatoid type. The coexistence of diabetes with rheumatoid arthritis is of particular interest in view of Pemberton's⁷ claims that the sugar tolerance is low in this form of joint disease. The following case illustrates the coincidence of diabetes and rheumatoid arthritis.

CASE REPORT (ABSTRACT)

Rheumatoid Arthritis and Diabetes

W L Male Aged 54

1925—Chronic sore throat Onset of diabetes 20 units of insulin daily
 1926—Gradual development of pain in knees and feet
 Jan 1930—Rapid onset of rheumatoid arthritis affecting many joints
 May 9, 1930—First seen by writer Many joints swollen Blood sugar 238 mg
 Urine showed trace of sugar
 June 6, 1930—Treatment for arthritis started vaccine, diet, etc
 June 13, 1930—Tonsils removed
 July 15, 1930—Joint condition improving steadily Blood sugar 200 mg Urine free from sugar
 Aug 6, 1930—Joints continue to improve Goes on a vacation
 November 1930—Patient died suddenly, cause unknown

TREATMENT

No discussion of the factors influencing recovery from rheumatoid arthritis would be complete without some consideration of the method of treating the disease. The method of treatment varies a great deal in different localities, and it would be beyond the scope of this article to discuss in detail these various methods of treating rheumatoid arthritis. There are certain fundamental phases of the treatment, however, that have an important influence on the course of the disease.

For example, with regard to foci of infection. A good deal depends upon *when* and *how* the focus in question is removed. For example, a focus removed early in the disease often leads to a permanent recovery from

the arthritis, while one removed two or more years after the onset of the joint symptoms rarely produces a favorable effect on the disease. Then so much depends on *how* foci are removed. The writer could cite more than one instance of sharp exacerbation of joint symptoms following tonsillectomy by an inexperienced or unskillful operator. I know of no operation where gentle handling of the infected tissue is more important. On the other hand I could cite one or two laryngologists who so far as I know have never produced a flare-up in an arthritic patient after the removal of tonsils. This has convinced me that good results following tonsillectomy depend a great deal on who removes the tonsils. Perhaps what has been said about tonsils applies even more in the case of surgery of the sinuses. Operations on the ethmoid and sphenoid cells are difficult at best and certainly require the utmost skill on the part of the operator if good drainage is to be established. In patients who have multiple root abscesses, it is better not to extract all the infected teeth at one sitting. Exacerbations in the joints have been known to follow such radical treatment.

If space permitted, a great deal could be said about the importance of cooperation on the part of the patient, and also concerning the choice of a physician. I would like to say one thing about the latter. I am not very sympathetic with the so-called arthritis specialist, that is, with the practitioner who devotes himself exclusively to treating this one disease. He will probably give his patients better treatment if he is a good all-round internist. I do say, however, that the patient with arthritis is wise if he seeks the counsel of a physician who is interested in this disease. The treatment of chronic arthritis, like that of the other great systemic diseases, presents a complex medical problem, and with it go the various specialized forms of therapy, such as control of diet, physiotherapy, intravenous vaccines, orthopedic measures, etc. Personally I believe that the time is not far off when every state in the Union will have specially equipped sanatoriums for the treatment of arthritis, similar to those which now exist for the treatment of tuberculosis. When that day comes, it is reasonable to believe that the chronic arthritic will fare much better than he does at present.

SUMMARY

In this brief discussion, I have tried to sum up the various factors which predispose to, and influence the course of, rheumatoid arthritis. We have seen that these factors may be either constitutional, such as race, temperament, heredity, sex, age or some constitutional disease, or they may be entirely environmental, depending on the economic status of the patient, his place of abode, the type of doctor he selects, and the kind of treatment he receives.

When we consider the multiplicity of factors which enter into recovery from this baffling disease, the need of concentrated and specialized care for rheumatoid patients becomes all the more obvious. In the opinion of the

writer, a considerable proportion of them should be treated in sanatoria especially equipped for the care of rheumatoid cases

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CARDIOVASCULAR OBSERVATIONS IN 215 NEUROSYPHILITICS *

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THE subject of this paper, cardiovascular syphilis, offers an interesting example of a tendency to search for the new while at times forgetting the old teachings. Aortic aneurysm appears after the introduction of syphilis into Europe subsequent to the return of Columbus and the occupation of Naples by the army of Charles VIII in 1495. Some sort of association with syphilis was mentioned by Fernelius in 1542, by Vesalius in 1557, and by Paré in 1582, who associated aneurysm with the "French disease." Morgagni (1682-1771) noted the association of aortic disease with syphilis. He first described a case of heart-block and what was later known as the Stokes-Adams syndrome. Then the luetic origin of aortic aneurysm was forgotten until nearly the middle of the past century, although Osler states that syphilis of the heart was mentioned as far back as 1736. French writers claim that Ricord, who was American born, first described definite cardiac gumma in 1845. However, accurate knowledge of cardiovascular syphilis is but little more than 50 years old, and 20 years ago there was practically no mention of the subject in current textbooks. There appears to have been a definite increase since the war and, either because of this or improved methods of diagnosis, it has occupied an important place in recent medical literature †

FREQUENCY OF CARDIOVASCULAR SYPHILIS

Numerous authors have discussed this subject with a wide divergence of opinion. The relation of cardiovascular syphilis to all forms of heart disease is given by Coombs¹ as 5 to 15 per cent and by Moore, Dangle and Reisinger² as 10 to 15 per cent. In general autopsy statistics cardiovascular syphilis appears according to different observers in 2 to 6 per cent of the cases examined. Aortic syphilis was observed at autopsy in late syphilis in 20.5 per cent of the cases examined by Coombs¹. Moore and his associates³ quote Langer, of Germany, to the effect that 70 to 80 per cent of all syphilitics show aortitis, aortic insufficiency or aneurysm, and that 50 per cent of all aortic insufficiency is syphilitic. Moore also advances the opinion that 80 to 90 per cent of all late syphilitics show evidence of aortic syphilis. Warthin^{4, 5, 6} teaches that aortitis with aneurysm or aortic insufficiency occurs in some degree in the aorta of every male syphilitic and,

* Read at the Chicago meeting of the American College of Physicians, April 19, 1934.
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† Since this was written, a most comprehensive review of the literature on cardiovascular syphilis has been presented by Dr. Lewis A. Conner in the Jr. Am. Med. Assoc., 1934, cii, 575, to which those interested are referred.

considering this frequency, that aneurysm and aortic insufficiency are rare occurrences in the history of aortic syphilis, and that these when present are due to functional stress. A more startling statement of the same author is as to the occurrence of syphilitic involvement of the heart. Briefly, this is that the spirochete is constantly present in the heart muscle of all cases of latent syphilis. In the congenital syphilitic heart the spirochete is demonstrated with some facility, but in the acquired form, while he states that the spirochete is constantly present, the demonstration of these organisms may require the utmost patience and considerable time—often weeks. Friedman⁷ quotes numerous authors as showing that vascular changes are noted in from 49 to 76 per cent of cases of visceral syphilis. The per cent in which thoracic aneurysm is syphilitic is given by Coombs¹ and Lendon⁸ as 75, and of abdominal aneurysm 35 by the former and 33.3 by the latter author. Moore and his coworkers³ state that 10 per cent of tertiary syphilitics show cardiovascular syphilis clinically but only 3.8 per cent of the cases of uncomplicated aortitis were correctly diagnosed antemortem, while according to Jagic⁹ only 2 per cent were clinically diagnosable. Grassman, quoted by Turner and White,¹⁰ found that in 288 cases of secondary syphilis arrhythmias or pulse disturbances were noted in 85 per cent and murmurs in 40 per cent. Amelung and Steinberg¹⁰ believe the above figures too high. They studied 275 early cases for one year and noted heart enlargement (confirmed by roentgen-ray), sound changes, tachycardia, premature contractions or murmurs, in 21 per cent. In this group was one case of aortic insufficiency, which was recognized clinically, and two proved at autopsy. Brooks¹¹ reports 2 cases of aortic aneurysm within six months of the primary lesion, and has in another report¹² recorded 24 of 300 cases of cardiac lues occurring in the secondary stage. Moore¹³ noted precordial pain of a few days' duration in a secondary case which subsided under specific therapy. But opinions differ widely. Turner and White¹⁰ report a study of 50 cases of primary and secondary syphilis, excluding all cases over 40 years to eliminate coronary sclerosis. There were no cases of hypertension or recognized arteriosclerosis and, so far as possible, other infections were excluded. They found no definite clinical evidence of cardiovascular disease and conclude that "a critical study of the literature shows that clinical evidence of cardiovascular disease in early syphilis is rare."

Wile and Marshall,¹⁴ Friedman,⁷ Lucke and Rea,¹⁵ et al., have called attention to an apparent selective affinity of the spirochete for certain tissues and to the fact that, dependent upon individual and racial differences, certain tissues appear to bear the brunt of the attack. Musser and Bennett¹⁶ describe a vasotrophic and neurotrophic strain of spirochetes.

CONCOMITANCE OF CARDIOVASCULAR SYPHILIS AND NEUROSYPHILIS

It is with this subject that the present study is especially concerned. Here again opinions differ widely as to the frequency of this association.

The frequency of occurrence of neurosyphilis in cardiovascular syphilis is given as follows Lendon⁸—10 per cent in whites, Riven and Feigenbaum¹⁷—10 per cent, White¹⁸—16 to 20 per cent with 33·3 per cent on pathological evidence, Coombs¹⁹ quotes Hubert as reporting 25 per cent of 300 cases of cardiac syphilis as also having tabes Moore² states that while not all patients with cardiovascular syphilis have tabes, practically all tabetic patients have syphilitic aortitis On this point—namely, the occurrence of cardiovascular syphilis in neurosyphilis—there is similar divergence of opinion from Friedman's⁷ statement of 10 to 20 per cent to Kurtz and Eyster's²⁰ report of the finding by fluoroscopic means of aortitis in 95·7 per cent and of aneurysms in 21·8 per cent of their cases of neurosyphilis In view of this wide difference, we concluded that an especial study of this relationship might explain this discrepancy and furnish an acceptable percentage of concomitance

PURPOSE OF THE PRESENT STUDY

- 1 To determine the frequency of cardiovascular syphilis in neurosyphilis
- 2 To determine the frequency of diagnosable cardiovascular syphilis in neurosyphilis
- 3 To determine the value of the electrocardiogram in the diagnosis of cardiovascular syphilis

MATERIAL

The data in this report are based upon a study of 215 cases of neurosyphilis in the Colorado Psychopathic Hospital at Denver between October 1929, and September 1933 These cases are divided into paresis, tabo-paresis, tabes dorsalis, and meningo-vascular syphilis as follows

| | | |
|-----------------------------|------------|---------------|
| A Paretics | 145 | 67·4 per cent |
| B Tabo-paretics | 15 | 6·8 |
| C Tabes | 18 | 8·3 |
| D Meningo-vascular syphilis | 37 | 17·5 |
| Total | <u>215</u> | |

Each case was further grouped as follows

- | | |
|-----------|---|
| Group I | Physical and roentgen-ray findings normal |
| Group II | Physical findings abnormal, roentgen-ray normal |
| Group III | Physical findings normal, roentgen-ray abnormal |
| Group IV | Physical findings abnormal, roentgen-ray abnormal |

Each case had a careful historical investigation, was examined by one or two physicians, and in all questionable cases by a consulting internist All patients showing any historical or clinical evidence of rheumatic heart disease (10 cases) were excluded, as were also five cases insufficiently

studied for inclusion in this series As a control group we studied in a similar complete manner 100 consecutive non-syphilitic cases in the same hospital

TABLE I

To show the age distribution of the entire group of 215 cases with reference to Groups A (Paretic), B (Tabo Paretic), C (Tabetic), D (Meningo-Vascular), and Classes I (Normal Physical), II (Abnormal Physical), III (Normal Physical), (Normal X-Ray) (Normal X-Ray) (Abnormal X-Ray) IV (Abnormal Physical) (Abnormal X-Ray)

| Groups | Totals | Ages 21-30 | | | | Ages 31-40 | | | | Ages 41-50 | | | | Ages 51-60 | | | | Ages 61-70 | | | |
|---------------------------|--------|------------|----|-----|----|------------|-----|-----|-----|------------|-----|-----|-----|------------|-----|-----|-----|------------|-----|-----|-----|
| | | I | II | III | IV | I | II | III | IV | I | II | III | IV | I | II | III | IV | I | II | III | IV |
| A PARETIC | | | | | | | | | | | | | | | | | | | | | |
| Number of cases | 145 | 9 | | | | 45 | 1 | 1 | 3 | 28 | 2 | 10 | 7 | 10 | 3 | 6 | 8 | 5 | 2 | 3 | 2 |
| Percentage of 215 cases | 67.4 | 4.1 | | | | 20.9 | 0.5 | 0.5 | 1.5 | 13.0 | 0.9 | 4.6 | 3.2 | 4.6 | 1.3 | 2.6 | 3.7 | 2.3 | 0.9 | 1.3 | 0.9 |
| B TABO-PARETIC | | | | | | | | | | | | | | | | | | | | | |
| Number of cases | 15 | 1 | | | | | | | | 3 | 1 | | | 4 | 1 | 1 | 2 | 1 | | | 1 |
| Percentage of 215 cases | 6.8 | 0.4 | | | | | | | | 1.3 | 0.4 | | | 1.8 | 0.5 | 0.5 | 0.9 | 0.5 | | | 0.5 |
| C TABETIC | | | | | | | | | | | | | | | | | | | | | |
| Number of cases | 18 | | | | | 2 | | | | 7 | | 2 | | 4 | 1 | 1 | 1 | | | | |
| Percentage of 215 cases | 8.3 | | | | | 0.9 | | | | 3.2 | | 0.9 | | 3.2 | 0.5 | 0.5 | 0.5 | | | | |
| D MENINGO-VASCULAR | | | | | | | | | | | | | | | | | | | | | |
| Number of cases | 37 | 4 | | | | 11 | | | 1 | 4 | 2 | 5 | 1 | 3 | | 2 | 3 | 1 | | | |
| Percentage of 215 cases | 17.5 | 1.8 | | | | 5.0 | | | 0.5 | 1.8 | 0.9 | 2.3 | 0.5 | 1.3 | | 0.9 | 1.3 | 0.5 | | | |

Table 1 shows

1 That a very large proportion (62.8 per cent) of these cases occur in the fourth and fifth decades and 6.3 per cent in the third decade before arteriosclerotic changes are of significance The average age was 45 years

2 That 33.9 per cent of the entire series occur among paretics between 31 and 50 (20.9 per cent 31-40) and that the cases included in this percentage are not diagnosed by physical or roentgen-ray methods

3 That 31.4 per cent of the syphilitic group occur after 50, 6.4 per cent of our controls fall in the fourth and fifth decades (31-50), 1.6 per cent before 30, and 2.0 per cent after 50

Of the 215 cases of neurosyphilis 73, or 33.9 per cent, showed some form of cardiovascular pathology independent of the electrocardiogram Of these 73 cases 57 were complicated and uncomplicated aortitis Of the remaining 16 cases three showed myocarditis without aortitis, five hypertensive heart disease, and eight were unclassified

Table 6, in which appears a summary of all autopsy reports on this complete series, presents a check on the accuracy of the clinical diagnoses Of the 14 cases coming to autopsy, in two only were the clinical findings not verified at autopsy, in these we failed to recognize an aortitis when present While this is a small number of autopsies it represents reports on 4.2 per cent of those who have died, and furnishes a fairly good check on the accuracy of the diagnosis of aortitis in this institution

TABLE II

Relationship of Aortitis and Aortitis with Complications to Electrocardiographic Changes

| Groups | Aortitis | Aortic Insufficiency with Aortitis | Aortitis with Hypertensive Heart Disease | Aortitis with Myocarditis | Aortitis with Aneurysm |
|--------|--|---|--|---|---------------------------|
| I | | | | | - |
| II | | | | | |
| III | Normal 8 Abnormal 9 Questionable 4 No EKG 7 Total 28 | | Abnormal 1 | | Abnormal 2 |
| IV | Normal 3 Abnormal 4 Questionable 2 Total 9 | Abnormal 4 Questionable 1 Total 5 | Normal 3 Abnormal 3 No EKG 2 Total 8 | Normal 1 Abnormal 1 No EKG 1 Total 3 | Questionable 1 |

Analysis of table 2 shows that no cases of aortitis were diagnosed save in the presence of roentgen-ray abnormalities, although 26 of 57 cases of aortitis showed in addition to roentgen-ray changes definite physical signs of heart disease. Table 2 further shows the frequency of electrocardiographic changes in each of these clinical groups. Uncomplicated aortitis shows electrocardiographic abnormalities less frequently than complicated aortitis, and when present these presumably indicate an associated coronary involvement sufficient to modify the nutrition of the heart muscle, although usually not sufficient to produce characteristic coronary changes.

Electrocardiograms were obtained on 47 of the 57 aortitis cases, and in 24, or 51 per cent, the curves were definitely abnormal, while in eight, or 17 per cent, the curves were considered questionable, making a total of 68 per cent of either abnormal or questionable electrocardiograms in this group of aortitis patients.

ELECTROCARDIOGRAPHIC STUDIES

The criteria employed were those approved by the American Heart Association²¹

In an earlier publication one of us (C T B)²² has shown that low voltage of R (not more than 5 to 8 mm) occurring in Leads I or II "is of sufficient value to be considered in connection with the prognosis of any cardiac case." This standard is less rigid than that of Sprague and White²³ and that of the Committee referred to in the foregoing paragraph. To avoid any criticism as to standards it has seemed preferable in the present study to adhere throughout to the accepted criteria.

The eight questionable abnormal curves (table 2) showed slurred R-waves in two cases, high R-wave in two, low R-wave in one, a questionable coronary S-T in one, slight left axis deviation in two, R-wave inverted in one, and T-wave inverted in one, but while all of these represented deviations from the normal, a conservative reading justified the interpretation of questionably abnormal rather than clearly abnormal electrocardiograms. Approximately 11 per cent, or every ninth, of all our curves fell in this class. In all cases of left axis deviation the habitus of the individual was considered and only those were regarded as abnormal in which the sthenic habitus could be excluded.

An electrocardiogram was obtained in 114 of the 145 paretics studied. Table 3 shows the distribution with reference to physical, roentgen-ray and

TABLE III

To Show the Distribution of 114 Paretic, 20 Tabetic and Tabo Paretic, and 30 Meningo Vascular Cases with Reference to Physical, X-Ray, and Electrocardiographic Changes

| Electrocardiograms | Physical and X-Ray Examination | | | | | | | |
|--|--|-------------|---|-------------|--|-------------|---|-------------|
| | Group I Normal Physical Normal X-Ray | | Group II Abnormal Physical Normal X-Ray | | Group III Normal Physical Abnormal X-Ray | | Group IV Abnormal Physical Abnormal X-Ray | |
| | Number of Cases | Per cent | Number of Cases | Per cent | Number of Cases | Per cent | Number of Cases | Per cent |
| <i>Paretics (114 cases)</i> | 72 | 100 0 | 7 | 100 0 | 19 | 100 0 | 16 | 100 0 |
| Normal | 48 | 66 7 | 2 | 28 5 | 8 | 42 1 | 4 | 25 0 |
| Abnormal | 17 | 23 6 | 4 | 57 1 | 8 | 42 1 | 9 | 56 3 |
| Questionable | 7 | 9 7 | 1 | 14 3 | 3 | 15 8 | 3 | 18 7 |
| Abnormal and Questionable | 24 | 33 3 | 5 | 71 4 | 11 | 57 9 | 12 | 75 0 |
| <i>Tabo Paretics and Tabetics (20 cases)</i> | 13 | 100 0 | 2 | 100 0 | 2 | 100 0 | 3 | 100 0 |
| Normal | 10 | 77 0 | 1 | 50 0 | 1 | 50 0 | 0 | 0 0 |
| Abnormal | 2 | 15 4 | 1 | 50 0 | 1 | 50 0 | 3 | 100 0 |
| Questionable | 1 | 7 6 | 0 | 0 0 | 0 | 0 0 | 0 | 0 0 |
| Abnormal and Questionable | 3 | 23 0 | 1 | 50 0 | 1 | 50 0 | 3 | 100 0 |
| <i>Meningo Vascular (30 cases)</i> | 18 | 100 0 | 1 | 100 0 | 6 | 100 0 | 5 | 100 0 |
| Normal | 10 | 55 6 | 1 | 100 0 | 0 | 0 0 | 2 | 40 0 |
| Abnormal | 6 | 33 3 | 0 | 0 0 | 5 | 83 3 | 2 | 40 0 |
| Questionable | 2 | 11 1 | 0 | 0 0 | 1 | 16 7 | 1 | 20 0 |
| Abnormal and Questionable | 8 | 44 4 | 0 | 0 0 | 6 | 100 0 | 3 | 60 0 |

electrocardiographic changes in this group of 114 paretics and also shows as follows

1 33 3 per cent abnormal or questionable electrocardiograms in paretics Group I

2 71 4 per cent abnormal or questionable electrocardiograms in paretics Group II

3 57.9 per cent abnormal or questionable electrocardiograms in paretics Group III

4 75 per cent abnormal or questionable electrocardiograms in paretics Group IV

We find that one-third of paretics without physical or roentgen-ray changes show an abnormal electrocardiogram, and this is abnormal much more frequently in the presence of physical, roentgen-ray or combined physical and roentgen-ray abnormalities. Abnormal physical signs appear to be more frequently associated with electrocardiographic changes than are roentgen-ray changes alone.

Twenty tabetics and tabo-paretics were similarly studied and in table 3 we show that in Group I, 23 per cent of the electrocardiograms are abnormal and, as in the paretic Groups II, III and IV, show a marked increase in the incidence of electrocardiographic abnormalities. Thirty meningo-vascular cases show 44.4 per cent electrocardiographic abnormalities in Group I. As in the paretics, tabetics and tabo-paretics an increase in electrocardiographic abnormalities is noted in the other groups, especially Group III, which shows practically 100 per cent abnormalities.

Especial interest attaches to the question as to what per cent of these cases, which were clinically normal from the cardiovascular standpoint, will show electrocardiographic abnormalities.

Table 4 shows 103 cases of central nervous system syphilis which on physical and roentgen-ray examination we considered normal from the cardiac standpoint.

TABLE IV

To Show the Incidence of Electrocardiographic Changes in Group I (Normal Physical and Normal X-Ray) in 72 Paretic, 13 Tabo-Paretic and Tabetic, and 18 Meningo-Vascular Cases

| Electrocardiogram | Group I Paretic Normal Physical Normal X-Ray | Group I Tabetic and Tabo-Paretic Normal Physical Normal X-Ray | Group I Meningo-Vascular Normal Physical Normal X-Ray |
|--------------------------------------|---|---|--|
| <i>Normal EKG</i> | | | |
| Number of cases | 48 | 10 | 10 |
| Per cent of cases | 66.7% | 76.9% | 55.5% |
| <i>Abnormal EKG</i> | | | |
| Number of cases | 17 | 2 | 6 |
| Per cent of cases | 23.6% | 15.4% | 33.3% |
| <i>Questionable EKG</i> | | | |
| Number of cases | 7 | 1 | 2 |
| Per cent of cases | 9.7% | 7.6% | 11.1% |
| <i>Abnormal and Questionable EKG</i> | | | |
| Number of cases | 24 | 3 | 8 |
| Per cent of cases | 33.3% | 23% | 44.4% |
| Totals | 72 | 13 | 18 |

Of the 72 paretics, 33.3 per cent showed abnormal or questionable electrocardiograms

Of the 13 tabo-paretics and tabetics, 23 per cent showed abnormal or questionable electrocardiograms

Of the 18 meningo-vascular cases, 44.4 per cent showed abnormal or questionable electrocardiograms

While the number of meningo-vascular cases is small as compared to that of the paretics the high percentage of electrocardiographic abnormalities is striking and suggests that the selective affinity of the spirochete for certain tissues discussed earlier in this paper may well explain this increased frequency of electrocardiographic abnormalities as compared with the paretic group

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS

Of 215 syphilitic cases, electrocardiograms were obtained in 164 and were abnormal or questionable in 47 per cent. Of 100 hospital control cases electrocardiograms were obtained on 100, and were abnormal in 33 per cent. Many of these changes were slight—especially in the control group—and included axis deviation and departures from the normal which could hardly be considered significant. Furthermore, in the syphilitic group multiple changes and changes involving all leads were much more frequent.

Our hospital control series consists of a group of 100 consecutive Psychopathic Hospital patients (average age 40 years) in whom there was no evidence of syphilis. Seven of these showed physical evidence of heart disease—a much higher incidence than in the general population. Therefore, we considered this an unsatisfactory control and planned a further control series. There were, however, no roentgen-ray changes in this control group. The high incidence of electrocardiographic abnormalities in these hospital patients is probably accounted for by the fact that they had undergone cardiac changes which would not be encountered in a control group of normal individuals.

Since this control series of hospital patients appeared in some respects to be unsatisfactory, we studied a second control series of individuals who were theoretically normal, although not comparable as to age.

One hundred medical students of an average age of 26 years (the extreme ages being 21 and 42) were submitted to physical, roentgen-ray and electrocardiographic examinations. Of these, 94 furnished normal electrocardiograms employing the same standards as have been mentioned in the preceding text. Eighty-five of these showing normal electrocardiograms were found normal on physical and roentgen-ray investigation, five showed physical abnormalities but normal roentgen-rays, and four presented physical or roentgen-ray abnormalities, but none of these was considered indicative of heart disease. In two fibroid phthisis was the

cause of cardiac displacement Of the group of five showing abnormal physical signs a definite cardiac diagnosis was made in three cases, in one mitral stenosis and insufficiency, and in two mitral insufficiency, but in the remaining two faint systolic murmurs at the apex, not transmitted, were the sole abnormalities and probably were of functional origin Of this group of 100 students there was therefore an incidence of clinical cardiac pathology of 3 per cent—a percentage in line with accepted standards

In the interpretation of the teleroentgenograms the small, the "asthenic" or the "drop" heart, the transverse heart and very slight right displacement, in the absence of other roentgen-ray or clinical evidence, were classed as normal

Of the 100 controls in this series only six showed abnormal electrocardiograms, but all of these appeared normal on physical and roentgen-ray examination In this connection it is interesting to note that the three individuals in whom a definite cardiac diagnosis could be made showed normal curves

In six of the 100 controls the electrocardiograms were considered abnormal In two there was abnormal right axis deviation without other change in the QRS complex, in one there was abnormal left axis deviation, in one abnormal left axis deviation with other changes in the QRS complex, in one T_{1+2} were low and T_3 inverted, and in one there was low voltage of the R-wave in all leads

The abnormalities noted in the six controls showing abnormal electrocardiograms are summarized as follows

| | |
|---|---------|
| Abnormal right axis deviation without other QRS changes | 2 |
| Abnormal left axis deviation without other QRS changes | 1 |
| Abnormal left axis deviation with other QRS changes | 1 |
| Low voltage of R_{1+2+3} | 1 |
| Low voltage of T_{1+2} with T_3 inverted | 1 |
| Total | <hr/> 6 |

Table 5 furnishes a comparison of the significant electrocardiographic findings in our patients falling in Group I and those of our two control series Ninety-three of the hospital control series would likewise fall in Group I since only seven of the 100 hospital control patients showed physical evidence of heart disease, and none of them roentgen-ray abnormalities Likewise 97 of our student control may be considered as comparable to Group I, since in all others showing abnormalities the physical or roentgen-ray findings were not considered to indicate heart disease We show that *R-S-T wave abnormalities, usually associated with coronary and myocardial changes, occur much more frequently in the syphilitic group, and that the coronary S-T curve occurs exclusively in this group* (9 cases) Because of multiple changes found in a single electrocardiogram, percentage comparisons as to the foregoing changes are confusing and therefore omitted Axis deviation was of no value in diagnosis

TABLE V

Electrocardiographic Findings in Group I (Physical and X-Ray Findings Normal) on 103 Cases of Central Nervous System Syphilis as Compared with Control Groups

| Electrocardiographic Findings | Central Nervous System Syphilis | | Controls | |
|---------------------------------|---------------------------------|----|-------------------|---------------------|
| | | | 93 Hospital Cases | 97 Medical Students |
| R-wave low | | 8 | 5 | 2 |
| R-wave slurred in Leads I or II | | 12 | 8 | 2 |
| T-wave changes significant * | High | 7 | 4 | 0 |
| | Low | 11 | | |
| | Inverted | 4 | | |
| Coronary changes ** | Unquestionable | 6 | 0 | 0 |
| | Probable | 3 | | |

* High T-wave or T-wave inverted

** Includes Pardee curve

We find that the greatest percentage of electrocardiographic changes occurs a decade earlier (fourth decade) in our syphilitic group than in the hospital control group of comparable age, suggesting an earlier cardiac involvement in syphilis

Leary and Wearn²⁴ have stressed the infrequency of coronary as compared to cerebral involvement in syphilis and suggest that where there is coronary closure, an adequate myocardial circulation may be maintained by means of the Thebesian veins, first demonstrated as far back as 1706 Pratt²⁵ likewise in 1898 showed the possibility of a blood supply from the ventricles directly to the heart muscle. We show a significant incidence of coronary involvement. The fact that many of these patients failed to present symptomatic evidence may be explained on the foregoing basis.

The percentage of abnormal electrocardiograms is higher in the syphilitic group (47 per cent) than in the hospital control group (33 per cent), and because of this high percentage in the control group we have presented a student control group showing only 6 per cent of abnormal electrocardiograms. Yet there was no significant change noted in the syphilitic group which was not found in the hospital control group with the sole exception of the coronary S-T change found in nine cases. It thus appears that while electrocardiographic changes occur in greater frequency in syphilis than in a control group of comparable non-syphilitic individuals, there is nothing sufficiently characteristic in the electrocardiograms of these patients to be of more than confirmative evidence when considered in association with the clinical findings in the case, but there will often occur evidence of coronary and myocardial change in the heart of the syphilitic patient not demonstrable by other than graphic means. The electrocardiogram is therefore of considerable value in the diagnosis and subsequent management of the patient.

PATHOLOGIC STUDIES

Thirty-three patients died and autopsies were obtained on 14 or 42 per cent

Table 6 shows that in Case 4726 a definite syphilitic aortitis was not diagnosed. In Case 5016 the evidence was not so clear, but the pathologist after considerable study classified this as syphilitic aortitis, likewise not

TABLE VI

Relation Between Physical Changes and Aortic Changes as Disclosed by Microscopic Findings

| Hospital Number | Age | Duration of Symptoms (Chancre) | Physical Findings | Microscopic Condition of the Aorta |
|-----------------|-----|--------------------------------|---|--|
| 3360 | 48 | 28 years | Negative | No evidence of syphilis |
| 3921 | 53 | ? | Negative | No evidence of syphilis |
| 5067 | 27 | 10 years | Negative | No evidence of syphilis |
| 3316 | 48 | 10 years | Negative | No evidence of syphilis |
| 3654 | 40 | 12 years | Negative | No evidence of syphilis |
| 4113 | 26 | 4 years | Negative | No evidence of syphilis |
| 4699 | 53 | ? | Negative | No evidence of syphilis |
| 3599 | 49 | 30 years | Negative | No evidence of syphilis |
| | | | | Some lymphocytic infiltration in adventitia. No definite evidence of syphilis, but suspicious |
| 5016 | 65 | 20 years | Negative | Marked lymphocytic infiltration of adventitia. Patches of necrosis of media. Fibrosis of intima. Syphilitic aortitis |
| 4726 | 39 | ? | Negative | Syphilitic aortitis |
| 5146 | 58 | 31 years | Aortitis, hypertrophy, hypertensive heart disease | Syphilis of aorta and aortic valves |
| 4184 | 61 | ? | Aortitis with aortic insufficiency | Syphilis of the aorta |
| 5496 | 48 | 25 years | Aortitis | Suggestive changes indicative of syphilitic aortitis |
| 4376 | 55 | ? | Aortitis, hypertension, myocardial insufficiency | Syphilitic aortitis |

diagnosed ante mortem. In the remaining 12 cases the antemortem diagnosis was confirmed.

CHANGE IN THE ELECTROCARDIOGRAM AFTER MALARIAL TREATMENT

The literature presents occasional cases of sudden death in the course of malarial treatment of paresis—in the absence of clinical evidence of heart involvement. Bach and Worster-Drought,²⁶ discussing this, state that at autopsy invariably aortitis or myocarditis was found. We find no reports in the literature of electrocardiographic studies of these cases, but Mikawa²⁷ and his associates studied the effect upon the electrocardiogram in patients inoculated with malaria in the treatment of gonorrhea. They showed some amplitude changes, especially in the S-wave in the course of the fever, and a transient conduction disturbance, but failed to state the duration of this disturbance. Thirty-nine of our malarial treatment cases had electrocardiograms before and after treatment, there was no change

in 54 per cent, a slight change in 28 per cent and a definite change in 18 per cent, but the duration and meaning of this change has not been determined

This is a very small group of cases but, excepting Mikawa's studies which were on six patients only, we appear to present the only existing information on the subject

Slight shift of the axis to the right after treatment was observed five times, was unchanged twice and disappeared in one instance. Thus in eight of 18 cases there was slight axis shifting, usually to the left. T-wave changes, especially in Leads II and III, either a tendency to flattening of the wave or inversion of the wave, were the only other changes at all frequent. Some change in the T-wave occurred in seven cases. Certainly this group is too small to justify any conclusions drawn from the foregoing observations

We have not attempted in this paper any consideration of the effects of treatment upon established cardiovascular syphilis, but will record the observation that two cases, 8 and 11, showed a significant diminution in size of the aorta following malarial treatment

THE EFFECT OF TREATMENT UPON THE INCUBATION PERIOD OF NEUROSYPHILIS

Considerable controversy is current as to the merits of early treatment of syphilis, especially the use of arsphenamine. Wilmanns and Steiner²⁹ hold that this treatment predisposes the syphilitic patient to the development of parenchymatous neurosyphilis, while Smith and Frankl³⁰ do not concur in this viewpoint. German and French workers³¹ have shown that the treatment of early syphilis has shortened the period of incubation in parenchymatous neurosyphilis whether treated with mercury or arsphenamine. Moore and Hopkins³² report that adequate and proper treatment of late nonsymptomatic neurosyphilis will prevent the development of clinical neurosyphilis. Hopkins²⁸ has pointed out that "inadequate treatment of early or late syphilis shortens the incubation period not only of tabes and dementia paralytica, but also of late meningo-vascular neurosyphilis." In this paper the term incubation period is used to denote the period elapsing between the primary lesion and the appearance of symptoms of neurosyphilis.

It is interesting to note that in this group of 215 proved cases of central nervous system syphilis only 72, or 30 per cent, gave a history of a chancre, of these 72, only 22 gave a history of some form of therapy.

In each case which gave a definite history of treatment we have attempted to gain a full history of the nature of such treatment. While in some few cases this was unsatisfactory, we feel that the majority of cases have related a complete history of their treatment. In none of these was the luetic condition adequately treated according to present day accepted

standards In keeping with this, we submit the following statement taken from one of the cases which is fairly typical

Chancre contracted in 1907, while in the Navy Treated in Naval Hospital in Brooklyn, given calomel and potash for a period of two months No further treatment until 1922 took four courses of four treatments each In 1928 took four treatments of neosalvarsan Some iodine was also taken at that time In January and March 1930, took six treatments of neosalvarsan, also had two Swift-Ellis treatments

With the past and present emphasis placed upon the need of early and adequate treatment of syphilis it is surprising that in our series only 10.2 per cent of the cases were treated, whereas Hopkins²⁸ reports 43 per cent

In Table 7 we present evidence to show that inadequate treatment of

TABLE VII

The Influence of Inadequate Treatment Upon Incubation Period of 72 Cases of Neurosyphilis

| | Paretics | | Tabo-Paretics | | Tabetics | | Meningo-Vasculars | |
|-----------------------------|----------|----------------------|---------------|----------------------|----------|----------------------|-------------------|----------------------|
| | Cases | Period of Incubation | Cases | Period of Incubation | Cases | Period of Incubation | Cases | Period of Incubation |
| Cases not treated | 29 | 16.97 years | 4 | 22.10 years | 6 | 20.30 years | 11 | 14.30 years |
| Cases inadequately treated | 14 | 14.20 years | 0 | | 4 | 10.50 years | 4 | 7.90 years |
| Total number of cases | 43 | | 4 | | 10 | | 15 | |
| Incubation period shortened | | 2.77 years | | | | 9.8 years | | 6.4 years |

early and late syphilis shortens the period of incubation of paresis, tabes dorsalis, and meningo-vascular syphilis In paresis this amounted to 2.77 years on the basis of 43 cases, in tabes dorsalis 9.8 years on the basis of 10 cases, and in meningo-vascular syphilis 6.4 years on the basis of 15 cases

THE EFFECT OF TREATMENT UPON THE TIME OF APPEARANCE OF SIGNS OF HEART INVOLVEMENT

We have also studied these cases from the standpoint of their cardiac changes The results are presented in table 8 Of the 50 untreated cases, 22 per cent were found to be abnormal on physical and roentgen-ray examination, while of the 22 inadequately treated cases 41 per cent were abnormal—that is, cardiac changes demonstrable by physical and roentgen-ray means were found approximately twice as often in the inadequately treated cases as in the untreated cases On the basis of 57 electrocardiograms performed on the 72 patients giving a history of syphilis, abnormal curves occurred more frequently in the inadequately treated group than in the non-treated group, although not to the same extent as above

Emphasis should be placed upon the potential danger of inadequate treatment in early and late syphilis as such treatment apparently interferes

TABLE VIII

The Contrast of Inadequate Treatment and No Treatment as Shown by Physical, X-Ray, and Electrocardiographic Changes

| Groups | Non-Treated Cases | | Inadequately Treated Cases | |
|-----------------------------|-------------------|----------|----------------------------|----------|
| | Number | Per Cent | Number | Per Cent |
| I Normal Physical and X-Ray | 39 | 78 | 13 | 59 |
| II, III, IV—Either Abnormal | 11 | 22 | 9 | 41 |
| Physical or X-Ray or Both | 50 | 100 | 22 | 100 |
| Totals | | | | |
| Normal Electrocardiogram | 24 | 60 | 8 | 47 |
| Abnormal Electrocardiogram | 16 | 40 | 9 | 53 |
| Totals | 40 | 100 | 17 | 100 |

with the resistance-building mechanism of the body and predisposes the patient not only to the development of neurosyphilis but of cardiac syphilis as well. At the present time we do not have sufficient data to report the incidence of neurosyphilis in adequately treated early cases of syphilis. Incomplete data indicate that the incidence is very low.

SUMMARY AND CONCLUSIONS

We have intensively studied a group of 215 cases of neurosyphilis in order to determine the frequency and type of cardiovascular involvement.

1 We find that 73, or 33.9 per cent, show some form of cardiovascular pathology, independent of the electrocardiogram.

2 Our findings are in agreement with others as to the importance of aortitis in syphilis, it furnishing the most frequent type of cardiovascular pathology in syphilis.

3 In association with syphilitic aortitis we find electrocardiographic abnormalities in 68 per cent of our cases.

4 33.3 per cent of our paretics, 23 per cent of our tabo-paretics and tabetics, and 44.4 per cent of our meningo-vascular cases, without physical or roentgen-ray abnormalities of the heart, showed abnormal electrocardiograms, and the electrocardiogram was abnormal in a much higher proportion in the presence of physical, roentgen-ray or combined physical and roentgen-ray abnormalities. Abnormal physical signs appear to be more frequently associated with electrocardiographic changes than are roentgen-ray changes alone.

5 We find a significant increase in electrocardiographic abnormalities in neurosyphilis, but no change which can be considered as characteristic of cardiovascular syphilis, although we are impressed with the incidence of coronary changes in our series.

6 The incidence of electrocardiographic abnormalities not associated with physical or roentgen-ray changes noted in this series of neurosyphilitics

justifies the routine use of the electrocardiogram in these cases as a means of an earlier recognition of cardiovascular involvement

7 The incubation period of neurosyphilis is shortened in paretics, tabetics, and meningo-vascular cases who have received early or late, but inadequate treatment

8 Cardiac lesions seem to be found more frequently in those cases inadequately treated. This is demonstrable by either physical, roentgen-ray, or electrocardiographic changes

9 There is definite need for more adequate therapeutic procedures in early and late syphilis to decrease the incidence of neurosyphilis

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ABDOMINAL PAIN· ITS SIGNIFICANCE AND DIAGNOSTIC VALUE^{*}

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THE diagnosis of intra-abdominal pathology is extremely difficult. We have no method for exact diagnosis such as the electrocardiogram for the cardiac lesion, the blood in primary anemias, the urine and functional studies in the nephritides and the sputum in pulmonary tuberculosis. We are helped a little in making such diagnoses by the study of gastric and duodenal contents, more by study of the stool, much more by fluoroscopy and radiography of the digestive tract. The physical examination of the abdomen is of course essential, often, however, in its interpretation puzzling and indefinite. Therefore, in many cases, in making a definite or potential diagnosis, we must depend upon the analysis and interpretation of the symptoms, the history of the case, its beginning, its evolution, upon our proper interpretation of these our final diagnosis often depends.

Few of these symptoms are diagnostic in themselves, for example, constipation may simply represent faulty habits of eating and living and be purely functional, but it may be the first sign of a colonic neoplasm or of some extra-gastrointestinal disease as, for example, unsuspected hypothyroidism, while an intractable diarrhea, usually of gastrogenous or enterogenous origin, may be the first and only symptom of the opposite condition—hyperthyroidism. Nausea, distress and vomiting may be of gastric or intestinal origin, but it may also represent the main symptoms of cardiac or renal disease, of gall-bladder pathology, or may be purely psychogenic—the mirror of a disturbed mind or the expression of maladjustment to the environment. But the symptom which most frequently brings the patient to the doctor, the symptom whose correct interpretation is most important in helping us to a correct diagnosis, is pain.

The cause of superficial pain is simple and easy to understand—specific pain nerves with exquisite localizing powers furnish a protective mechanism to external trauma and are essential to the preservation of the individual and the evolution of the race. The cause of visceral pain is not simple and is not easily explained. There are no such specific pain nerves as are met with in the skin and no need for them as the viscera are protected against external trauma by the bony and muscular cage which encloses them. The normal physiology of digestion proceeds automatically and autonomically. Health is spelt by a proper balance between two opposing sets of impulses—one stimulating, one inhibiting, pain or discomfort probably represents lack of balance in this mechanism, usually secondary to organic pathology in the viscera themselves. And thus, what we interpret as pain, in reality probably represents change in intra-gastric or intra-intestinal pressure, increased tonus, or hyperactive peristalsis.

^{*} Read at the Chicago meeting of the American College of Physicians, April 20, 1934

Most investigators feel that there are few, if any, true pain fibers in the nerves supplying the abdominal organs. We know, for instance, that the viscera can be crushed or burnt or pressed upon with great force without any pain, though Langley and Gaskell believe that there are a few medullated sensory fibers in the splanchnics. These must be very few, if any, because of the obvious lack of sensation of the viscera in the ordinary sense and the extreme paucity of the afferent fibers in the nerves supplying the abdominal organs. We know that the visceral peritoneum is devoid of pain fibers. Capps believes that true sensory fibers may exist in the parietal peritoneum which may give rise to pain and to some extent localize it, but most physiologists think that in the parietal, as in the visceral, peritoneum there are no true pain fibers and that discomfort or pain produced by pressure is brought about by sensations arising from the rich nerve supply of the loose connective tissue external to the parietal peritoneum.

Certainly the weight of evidence is in favor of the view that there is almost complete absence of true pain receptors in the visceral walls. Many physiologists believe that hypertonus, increased pressure, and overactive peristalsis are the causes of so-called abdominal pain, that impulses may arise in afferent nerve endings of the viscera as a result of stretching or compression, that this pain is not localized but is usually referred to certain areas in the surface of the body and may be associated with superficial or even somewhat deeper sensitiveness of the cutaneous and muscular covering. But this explanation, while fairly satisfactory as regards the intestine, is not enough to explain the pain met with in certain other portions of the abdomen, notably the stomach. Here we must presuppose that the disease produces a very definite hypersensitiveness, possibly the development of irritable foci in certain regions of the spinal cord due to repeated abdominal impulses, possibly a local hypersensitiveness to any form of stimuli at the seat of the lesion itself as well.

Thus, in our analysis of the causes of abdominal pain, perhaps our best explanation is that abdominal impulses may result in referred pain—the viscerosensory reflexes—tenderness, that is cutaneous or muscular hyperalgesia, muscular contractions, that is muscle spasm or *défense musculaire*. Possibly certain sensations are due to a lowered threshold of pain or to hypersensitiveness in the lesion itself or in that area of the spinal cord connected with the lesion through its nerve supply.

Thus, abdominal pain is a very complex phenomenon and its interpretation may be made difficult by many confusing factors—the similarity of the nerve supply to many of the abdominal viscera as well as to certain contiguous organs such as the heart and lungs, the diversity of the paths through which painful sensations may leave the abdomen, the proximity of the visceral organs to each other—one's hand can almost cover gall-bladder, pylorus, duodenum and a segment of the transverse colon, while the thin diaphragm alone separates heart and lungs from liver, stomach and spleen. Perhaps an even more difficult factor in the interpretation of pain is the

enormous variation in the picture due to individual variation in response to stimuli

In analyzing and interpreting abdominal pain, we have to consider all of these factors—physiological imbalance, organic pathology, congenital or acquired, local or general hypersensitiveness, the overlapping and confusion of symptoms due to similar nerve supply and close proximity of organs, the whole modified to a tremendous degree by the emotional stability or instability of the patient

At the present time, this last factor has been given perhaps undue prominence. It is the fashion of the age to explain complaints on a purely psychogenic basis—emotional instability, lack of insight, maladjustment—and to advise a treatment based upon such a conception—reeducation, psychotherapy, the removal or minimization of psychic strain. This is a dangerous attitude of the mind as regards abdominal pain, for while minor discomfort may be exaggerated into exquisite pain by the neurotic, and all forms of pain may be simulated by the auto- or hetero-suggestion of the hysterical, these are usually recognized and properly interpreted by the competent physician. True abdominal pain usually means organic pathology and its underlying basis is usually structural change. It is a very dangerous thing to diagnose gastralgia or enteralgia and to ascribe to a psychasthenic state symptoms associated with true pain, especially if associated with rise of temperature, with local tenderness, with an increased leukocyte count. Too often such an interpretation will lead to deplorable delay and the appendix ruptures or an ulcer perforates while the patient is being treated on the assumption that the condition was purely functional.

In the interpretation of pain, its evolution, its localization, its radiation, its character, its constancy or its irregularity, its periodicity, there are certain general principles which one should never forget. First, that the pain is a summation of local pathology, organic or functional, and psychic response, thus a mild lesion in a psychasthenic individual may elicit much more complaint than a far more serious lesion in a stable person. Second, the size or extent of the lesion has absolutely no relation to the severity of the pain. A pin point erosion of the mucous membrane can produce as much pain as a deep callous ulcer, a small gall-stone usually gives much more pain than a large one, a gastric ulcer and even a duodenal ulcer may give no pain whatsoever, pain is absent in many cases of cancer of the stomach. It is the tragedy of cancer that pain is not an early symptom, often not even a late symptom, when it appears it usually represents the beginning of obstructive symptoms rather than anything integral to the growth of the cancer itself. Third, while the disappearance of pain usually means improvement, sometimes the reverse is true, as in a gangrenous appendix or gall-bladder.

There are certain pain patterns which we should never forget and which are almost diagnostic—pictures which give us our probable diagnosis from the history of the patient alone. Such is the pain of duodenal ulcer, with its relief by food, its periodicity, and its punctuality. Moynihan used to

say he could set his watch by the hunger pains of his patients, while as regards its periodicity, we all know that spring and fall are the times of election. Such also are the agonizing attacks of upper right quadrant colic with radiation to the right shoulder, so often met with in cholelithiasis and peculiarly likely to occur during the wee small hours of the night, the discomfort or cramp-like pain, beginning in the epigastrium and finally localizing in the lower right quadrant, of acute appendicitis, with its local tenderness, its muscle spasm, its constipation, nausea, fever and increased leukocyte count, the agonizing pain with circulatory collapse of acute pancreatitis and the somewhat similar picture of perforated ulcer with absence of early collapse, the periodic cramp-like pains due to intestinal obstruction, whatever its cause.

These are clear cut clinical pictures, where the location of the pain, the type of pain, the history of the pain, often without the associated clinical and laboratory findings, give us as a rule a definite diagnosis. But we must never forget that each one of these can be simulated by intra- or even extra-abdominal conditions in a certain small proportion of cases. Renal colic may absolutely simulate biliary colic, duodenal ulcer may occasionally give the picture of a gall-stone attack, while ulcer, gall-bladder disease or appendiceal disease may be simulated by a great number of other conditions which we will briefly touch upon later also. Every one of these conditions, which as a rule have such characteristic histories, may in certain instances have no local symptoms whatsoever, only symptoms referred elsewhere. For instance, in acute appendicitis, the pain may persist in the epigastric region, it may be only umbilical in location—this in about 5 per cent of the cases, it may simulate a gall-bladder attack or may produce pain only in the back or in the pelvic region or down the right leg.

In many other abdominal conditions, the pain picture or pattern may be suggestive, but not diagnostic. It is blurred, it is confused, as for instance in many cases of gastric ulcer, in a small number of cases of duodenal ulcer, in a larger number of cases of biliary tract disease, and in a considerable number of cases of intestinal obstruction due to neoplasm, postoperative adhesions, etc., where the symptoms are too often explained on a purely functional basis and operation often delayed far too long, especially in the malignant type of obstruction. The diagnosis of chronic appendicitis is unquestionably erroneous in the majority of cases, but it is justified in a small percentage of cases where the pathologic signs are in the lower right quadrant and the referred pain usually in the epigastrium though occasionally in the upper left quadrant.

We have not time, of course, to discuss in detail the many other intra-abdominal conditions where the pain is referred elsewhere in the abdomen or the innumerable cases of disease outside the abdominal cavity where one of the symptoms, sometimes the main symptom, occasionally the only symptom, is abdominal pain, but I do wish to mention certain of these that have

been singularly interesting to us in our very intensive study of abdominal pain over a long period of years

Let us first discuss briefly certain of the more puzzling examples of referred abdominal pain

True angina pectoris may present no symptoms above the diaphragm, only violent epigastric pain, without radiation. This unfortunately is only too often diagnosed as an acute indigestion and treated by purgatives and exercise, when morphia and rest may be the only means of saving life. Also a few cases of coronary thrombosis so exactly simulate gall-stone colic that gall-bladders, usually quite normal, have been removed on this false hypothesis. It is well to remember that in a very few instances the reverse of this picture is true—that is, unsuspected gall-bladder disease may present symptoms absolutely simulating attacks of stenocardia or coronary thrombosis. It is also well to remember that rare cases of carcinoma of the liver, and, somewhat more frequently, cases of hepatic cirrhosis may present, during their course, attacks absolutely simulating gall-stone colic, frequently incorrectly confirmed by Graham gall-bladder pictures. In reality the attacks represent no disease of the gall-bladder but acute infections or reinfections of the previously diseased liver.

Perhaps the best explanation of this correlation between cardiac and biliary phenomena is that given by Head: "When a painful stimulus is applied to a part of low sensibility in close central connection with a part of much higher sensibility, the pain is felt in the part of higher sensibility rather than in that of lower sensibility to which the stimulus is actually applied."

This also may be the explanation of the acute abdomen often simulating appendicitis which is met with occasionally in central pneumonia and diaphragmatic pleurisy.

While in many cases the peptic ulcer syndrome may require for its explanation a local hypersensitiveness to irritants, such as acid, or a general or central hypersensitiveness so often associated with emotional crises or psychic strain, nevertheless the bulk of the evidence favors the view that pyloric spasm, increased intragastric pressure, hypertonus and hyperperistalsis play the major rôle in its production. These motor disturbances can be produced so easily by referred impulses from disease elsewhere that it is not surprising that ulcer is often diagnosed in disease of many other organs. For example, in tabes dorsalis, where an Argyll Robertson pupil and absent knee jerks should have given us our clue, although unfortunately it is not infrequent that this clue is overlooked and even surgical treatment employed, in renal or urinary calculus where the urinary findings and a flat plate of the abdomen should have given us our diagnosis, in certain cases of gall-bladder disease where x-ray plates by the Graham method may help us, or in obstruction of the colon, whether benign or malignant, where there are no local symptoms, only those referred to the stomach. Of course in carcinoma of the colon or in obstruction due to other causes, this is not

the usual picture, and the pain, while not definitely localized, is usually in the lower abdomen, usually spasmodic, often with surprisingly long intervals between attacks, and generally misinterpreted for a long period of time. In reality everyone presenting such a syndrome should make us suspect early malignancy, especially in older people, and should set in motion that set of diagnostic procedures—palpation of the abdomen in a hot bath, fluoroscope of the colon by the barium enema, digital rectal examination, study of the stool for occult blood—that should either confirm or refute this suspicion.

A small epigastric hernia may produce pain absolutely similar to that of ulcer, and the same may be true of herpes zoster before the appearance of the eruption, although here, as a rule, the pain is much more likely to simulate acute appendicitis. Lower right quadrant pain simulating sub-acute or chronic appendicitis is met with in such a varied group of diseases elsewhere that it would be remarkable if incorrect diagnoses were not singularly likely to occur with this syndrome. Right-sided pyelitis, especially in young female children where the urine may be clear due to the plugging of the ureter on the infected side, true ureteral stricture (a rare condition), right salpingitis, ovarian cyst with twisted pedicle and tubal pregnancy, all present pictures suggestive of appendicitis, but usually differentiated by careful examination.

Perhaps equally interesting and certainly more puzzling is the picture suggesting an acutely diseased appendix met with in certain of the infectious diseases—notably measles before the appearance of the eruption, typhoid fever in its early stage, acute follicular tonsillitis, influenza, in a few instances even scarlet fever and undulant fever, the latter showing a peculiarly puzzling picture when it has mainly abdominal manifestations. Perhaps the best explanation in many of these cases is a marked localization of the infectious agent in the rich lymphoid tissue about the cecum. In this connection, we know that tuberculous or nontuberculous adenitis, localized in this area, may absolutely simulate appendicitis, while allergic phenomena, such as we meet with in angioneurotic edema or in Henoch's purpura, may present a similar lower right quadrant picture. Perhaps the most difficult of all to explain is the acute abdomen, usually simulating acute appendicitis, sometimes found in sickle cell anemia.

Space does not permit us to call attention to other rare causes of abdominal pain with which we have met. Each of these presents its own special problem, where a correct diagnosis is often singularly difficult, sometimes impossible, as for instance, chronic pancreatitis in the aged, a much neglected diagnosis, with epigastric pain, usually mild, the puzzling abdominal pain of arthritis of the spine, of aneurysm of the renal artery, of a psoas abscess or of a burrowing abscess secondary to a diverticulitis, of tuberculosis of the mesenteric or retroperitoneal glands, of an unsuspected localized osteomyelitis, mesenteric thrombosis, atypical ileus and chronic intussusception.

Each of these presents its individual problem, but in most cases this is capable of solution if the diagnostic procedure is thorough and the reasoning of the clinician logical.

In the solution of each of these abdominal problems, we must of course utilize every diagnostic procedure. We must take a careful and complete history, make a thorough physical examination, and utilize to the full the findings from the clinical and x-ray laboratories, but in almost every case, the pain picture is a valuable, often an invaluable, aid, while sometimes it is the only key that will unlock the closed door.

True clinical research is far more difficult than laboratory investigation, but if done scientifically and thoroughly by one who knows the art, as well as the science, of medicine, it is equally productive of results. In clinical research there is no more promising field than that of the interpretation of abdominal pain. It is a very difficult field—the picture often blurred, pain patterns overlapping because we are not analyzing pictures produced by true visceral pain fibers but are trying to interpret physiological dysfunction.

Sometimes the problem is insoluble, sometimes we have to say with Charles Mayo that it is not knowledge of anatomy and physiology which teaches us the significance of a certain pain, but experience with that same type of pain observed many times before, and what was found when the abdomen was opened. But in the majority of cases, the careful analysis of pain gives us valuable information and it may be the only solution to the diagnostic puzzle.

Are we trying to turn back the hands of the clock? I do not think so. We are simply repeating what Gowland Hopkins, the President of the Royal Society of London and the most distinguished research student in his own field, has said: "Experience at the bedside and the habit of close observation are essential for the making of a successful physician." We are simply stating that at the present writing the science of medicine alone, the results of clinical laboratory and x-ray studies, at least in the abdominal field, are not sufficient to lead to a correct diagnosis in most cases. It means we must not discard the art of medicine, and that the microscope, the test tube, the instruments of precision and the x-ray cannot as yet displace the eye, the ear, the finger, and the results of observation.

There is unquestionably too great a tendency at the present time to lean too heavily upon laboratory methods and too lightly upon pure clinical observation. If we recognize this imbalance and, while not neglecting the results of laboratory methods which are invaluable, attempt to recapture the marvelous clinical sense, the wonderful powers of observation, analysis and deduction of Bright and Addison and Sydenham, of Osler and Thayer, perhaps we may reach the point where we can say with Edmund von Neusser, the greatest clinician of his day, that "The history of the case should give us our correct diagnosis, the physical examination and laboratory tests should be merely confirmatory"—or even be able to confirm what Hilton said many decades ago—"Every pain has its distinct and pregnant significance if we will but carefully search for it."

FACTORS INFLUENCING OPERATIVE MORTALITY IN EXOPHTHALMIC GOITER *

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DURING the past 50 years much has been written about the surgical management of patients with toxic goiter. Just before the introduction of iodine 12 years ago, the operative mortality had shown a steady reduction with increasing experience until, in the best clinics, it varied from 1 to 4 per cent. Not only had the mortality as a whole shown a marked reduction, but the mortality record of every thyroid surgeon had shown a marked decrease as his experience increased. This drop in the mortality rate may be attributed to two factors: (1) increase in surgical skill and improvement in technic, (2) improvement in surgical judgment. Surgeons gradually had learned when to operate and when not to operate and what surgical procedures their patients would tolerate. They had learned not to operate when the disease was increasing in severity, that the presence of marked emotional instability meant that it was unwise to attempt surgery, that the production of a gain in weight by the administration of a high caloric diet was a favorable sign, that psychic traumata exaggerated the disease and hence should be avoided, and that all of the signs and symptoms of the disease diminished in intensity with rest. Most surgeons moreover had agreed that it was wise to perform the thyroidectomy in several stages in the more severe cases. It is of some interest that, as a result of the application of these principles, the mortality in the clinics of the best thyroid surgeons was lower before the days of iodine than the mortality in many clinics at the present time.

Following the demonstration of the marked beneficial effects of iodine in exophthalmic goiter by Plummer, there was a tendency in some quarters to ignore the lessons learned before its introduction and to place too much reliance on iodine. It was said that iodine abolished crises and the need for multiple stage operations. It became rather common to say that the treatment of exophthalmic goiter consisted in the administration of iodine for about 10 days, followed by the performance of a subtotal thyroidectomy. It gradually became apparent, however, that some patients were still dying of typical thyroid crises after operation and that some patients died even before operative procedures could be carried out, in spite of the administration of large doses of iodine and the institution of other therapeutic measures known to be of value. The past few years have, therefore, been characterized by a growing realization of the importance of factors found

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to be of value before the days of iodine and by a more precise evaluation of the effect of iodine. The result is that we have come to regard iodine as a great help in preparing patients for operation, which must be used, not alone, but in conjunction with every other worthwhile therapeutic procedure.

The various factors of importance in the successful management of patients with toxic goiter may be discussed under the following headings:

- 1 The skill of the surgeon

- 2 Selection of the time and type of operation, with special reference to emotional instability, iodine, diet and rest

- 3 Treatment of complications

- 1 *The Skill of the Surgeon* In the successful outcome of all operative procedures surgical skill is a factor, and this is particularly true of thyroidectomies for exophthalmic goiter. In our experience, severe postoperative reactions and various complications of thyroidectomy have always been more common following surgical procedures carried out by inexperienced men than after those carried out by experienced men. We have repeatedly seen severe postoperative reactions follow hemithyroidectomies by inexperienced surgeons in patients that would probably have had mild reactions following subtotal thyroidectomies by experienced surgeons. We recall one young surgeon of little training who performed a thyroidectomy on a patient with exophthalmic goiter who had the disease in fairly mild form and in whom the emotional instability was not marked. From our observations, we predicted that the patient would have a mild postoperative reaction. Nevertheless, for 12 hours after operation, her pulse rate varied from 150 to 160 per minute and she was unduly sick. After this, and at about the time when the postoperative reaction usually becomes severe if it is going to, her pulse rate dropped markedly and she began to improve. Such a reaction we are inclined to attribute to direct trauma caused by unnecessary manipulation and prolongation of the operation through lack of surgical skill. We have pointed out elsewhere how the mortality rates of all prominent thyroid surgeons have steadily dropped with increasing experience. Men who become proficient in goiter surgery by doing large numbers of thyroidectomies over a long period will undoubtedly continue to have lower mortality rates than general surgeons who do a comparatively small number of thyroidectomies.

- 2 *Selection of the Time and Type of Operation* It has been rather generally taught that a thyroidectomy should be performed as soon as the basal metabolism shows a maximum reduction, namely about 10 days after the administration of iodine is started. In recent years, we have departed somewhat from this dictum and have made it a point not to have patients operated on until we thought they were ready, regardless of how long operation needs to be postponed. It has been our experience that maximum improvement does not occur as soon as the basal metabolism has shown a maximum reduction, but only some time later, when the patient has had an opportunity to derive the benefit of the lowered rate of metabolism. In

gauging the ability of patients to withstand operative procedures, we pay most attention to the intensity of emotional instability. The severity of the postoperative reaction more closely parallels this factor than any other, a fact pointed out by Plummet years ago. If, in spite of a well marked reduction in basal metabolism, the patient still thrashes about in bed and weeps at frequent intervals, it is probably unwise to attempt operation. We have reported elsewhere¹ data on two patients which illustrate the importance of considering emotional instability. One was a girl of 17 whose basal metabolism was plus 108 per cent on admission to the hospital. With rest and iodine the rate dropped to plus 32 per cent and her pulse from 125 to 71. However, marked emotional instability persisted up to the time of operation. Laughing would alternate with weeping for no apparent reason. The morning of the operation she wept violently. She was operated on after the conventional period of iodine administration and had lost no weight after admission to the hospital. At no time during operation did her pulse rate rise above 88, yet she died 48 hours after operation of an intense thyroid reaction. A large thymus was found at autopsy which may or may not have been related to her death according to the Graves' constitution theory of Warthin² and others. The other patient was a man of 50 whose basal metabolism dropped only slightly (from plus 46 per cent to plus 33 per cent) during the administration of iodine. Although he gained 2.5 kg. in weight before operation, the nervous manifestations of the disease persisted in a severe form and we were skeptical about his ability to withstand surgery. Nevertheless, he took the anesthetic well and it was decided to proceed with a subtotal thyroidectomy. He died about thirty hours after operation of a thyroid crisis complicated by bronchopneumonia.

This raises the question of the importance of the basal metabolism in gauging the operative risk. On the average, the lower the basal metabolism the better the operative risk, but there are many exceptions to this rule. We have seen only moderately severe postoperative reactions in patients in whom the basal metabolism showed no reduction during the administration of large doses of iodine and remained at a level of from 50 to 60 per cent above normal, while we have seen other patients die whose basal metabolism was only from 20 to 30 per cent above normal at the time of operation. The first group of patients were comparatively calm and the second group unstable emotionally and it is the intensity of this factor which seemed to be related to the severity of the postoperative reaction.

Contrary to the generally accepted teaching, the basal metabolism will rise very little in most cases during the administration of iodine if operation is delayed from two to three weeks beyond the time of maximum reduction. The danger of a rise in metabolism during several weeks of treatment with iodine with the patient at rest in bed in the hospital, has, in our opinion, been overemphasized. If the metabolism does rise slightly we ignore it in gauging the probable outcome of the operation. In a few cases, however, the metabolism rises rapidly after an initial drop in spite of the administration of iodine.

and sometimes to a higher level than before iodine was started. Associated with this rise in metabolism is an increase in the intensity of all the manifestations of the disease, including the nervous manifestations. Unfortunately this rise tends to occur in the patients who have the disease in the more severe form, that is in just those patients who need the benefit of rest most. This raises the problem of refractoriness to iodine and its management. We have reported elsewhere³ two patients who became partially and completely refractory respectively to about 6 milligrams of iodine daily in the form of Lugol's solution during its prolonged administration and who, after periods of omission of from 30 to 60 days, again showed a well marked response to it. It has never been conclusively established that patients become completely refractory to much larger doses of iodine after showing an initial response, although it is likely that this occurs, because a certain percentage of patients initially show no response to iodine. The main problem is whether the refractoriness is caused by the iodine itself or by a spontaneous variation in the intensity of the disease. If the iodine is responsible, then it should be omitted, whereas if the nature of the disease itself is responsible, then iodine should be continued, because many patients develop only partial and not complete refractoriness to it. While this point is yet unsettled, we do know that if the metabolism is rising rapidly it is usually safe to omit iodine and that after a period of omission, patients will usually respond to it again. The administration of enormous doses of iodine (100 minims of Lugol's solution daily) during the refractory period is of no more value than the administration of much smaller doses, although teaching to the contrary persists. It is probable that 5 minims of Lugol's solution daily always produces a maximum effect. We have observed previously⁴ about as much effect on metabolism in Boston during the administration of 1 minim of Lugol's solution daily as Lerman and Means⁵ did during the administration of 90 minims daily. We routinely use 10 minims of Lugol's solution three times a day. This dose is used partly as a matter of habit and partly to prevent criticism on that score by surgeons when they have poor results. The form in which iodine is administered is not of great importance. Sodium iodide and potassium iodide possess the advantage over Lugol's solution that they are more palatable. Iodine has no effect on the secretion of the thyroid after it leaves the gland. It is, however, given routinely after operation because in a varying percentage of cases (from 5 to 15 per cent), depending upon the surgeon, enough thyroid tissue is left at operation to cause the disease to persist in a subdued form. Since it is impossible to predict at the time of operation just which cases these will be, it is necessary to administer iodine post-operatively to all patients in order to control the thyrotoxicosis in the few instances in which it persists.

Muscle weakness is one of the characteristic findings in exophthalmic goiter and when marked, as judged by inability to climb up on a chair without assistance, usually means that operative procedures will not be well

tolerated. Marked muscle weakness and marked emotional instability usually but not always go hand in hand. It is a matter of experience that these two manifestations of the disease, like all the others, usually decrease in intensity with rest. Thyroidectomies for exophthalmic goiter are not emergency operations and if done as such, kill a large percentage of the patients operated upon. We therefore, make it a point to delay operation until we think the patient will stand it. During this period we keep the patient in the hospital and continue the administration of iodine. Rest is not complete and the usual ambulatory privileges are allowed, except in the presence of extreme muscle weakness or cardiac decompensation.

We have virtually abandoned the ligation of arteries as a surgical procedure in exophthalmic goiter because it appears to have no influence on the course of the disease. Its only indication would appear to be to test the ability of the patient to withstand more extensive operative procedures when there is any doubt about this, and it should be possible to gauge this in other ways. It has the disadvantage that it produces unsightly scars and often renders more difficult the technic of a subsequent thyroidectomy. It is the impression of most workers in the field that the severity of the postoperative reaction is directly related to the extent of the surgical procedures, that is, the amount of tissue removed. Lahey⁶ has said that hemithyroidectomies should be done in all patients in whom there is any doubt about the ability to withstand operation. Richter⁷ does not agree with this point of view and feels that his low mortality, even before the days of iodine, may be attributed to the fact that he left very little thyroid tissue to cause any reaction. If, in spite of the various precautions outlined, the patient still seems to be in poor condition for operation, roentgen-ray treatment may be used. This has to be carried out with caution in severe cases. Although it may not cure the disease, it usually reduces its intensity sufficiently to permit a thyroidectomy to be done with safety.

It is important to bear in mind that exophthalmic goiter is a disease in which body tissue is broken down at a rapid rate. It is reasonable to assume that the prevention of this breakdown is a desirable therapeutic procedure. It has been our experience that a well marked gain in weight before operation is a favorable prognostic sign. If combined with a well marked reduction in basal metabolism a satisfactory outcome of the operation is almost assured. In order to make the patients gain weight, it is usually necessary that the caloric intake exceed the basal caloric expenditure by at least 100 per cent. This means that most patients should receive from 4000 to 5000 calories daily. Such a diet invariably assures an adequate protein intake to offset the high nitrogen excretion often present in the disease.

By administering a meal consisting largely of carbohydrate four hours before operation the danger of the development of acidosis shortly after operation is reduced. Such a meal may consist of 250 c c of orange juice and an average sized helping of oatmeal with milk. A dose of iodine

should be administered with the meal. Such a meal will usually be out of the stomach by the time of operation. For a few days following operation, the caloric expenditure of the individual, which was already high before operation, is still further accelerated. Hence the caloric intake should be maintained at as high a level as possible in the immediate postoperative period. This is usually most conveniently done by administering a mixture of equal parts of milk and cream, which should be begun as soon as vomiting ceases.

Patients who are in good condition before operation can withstand vomiting of from eight to 10 hours' duration without a serious drain on the body reserves. Should vomiting continue beyond this time, fluid should be administered subcutaneously in the form of 10 per cent glucose at the rate of 3000 c c in 24 hours. This not only provides fluid but prevents the development of an acidosis. The glucose should contain iodine in any suitable form. The patient should receive at least one dose of iodine in the 12 hour period immediately following operation. Rarely is it necessary or desirable to give fluid intravenously after operation. Whenever the circulation is so poor that fluid is not absorbed from the subcutaneous spaces, the condition of the patient is usually so critical that putting it directly into the circulation will not accomplish the desired result and has the further disadvantage of overloading the right side of a heart which is already failing. Moreover, when reactions occur, as they do occasionally even in hospitals where great care is used in the preparation of glucose, they are less apt to be fatal if the injection has been given subcutaneously than if it has been given intravenously. What has been said about the intravenous administration of glucose applies also to the intravenous administration of normal salt solution and various iodine preparations. The majority of patients do not require the parenteral administration of fluid. We have seen patients who were in excellent preoperative condition, and who otherwise would have had mild postoperative courses, suffer greatly because of reactions following the parenteral administration of fluid on a standing order. We know of several instances in which the needless administration of fluid by the subcutaneous and intravenous routes appeared to be a factor in the death of patients. In the postoperative management of our patients we deal with many different interns on many different services and our chief trouble is not to get them to do enough, but to keep them from doing too much.

3 Treatment of Complications **Cardiac Irregularities** The indications for thyroidectomy are virtually the same when cardiac irregularities are present as when they are absent. This means that in the absence of other untoward signs, we ignore cardiac irregularities in gauging the risk of operation. Auricular fibrillation in particular is common, both preoperatively and in the immediate postoperative period, and is of itself almost never a cause for alarm. Transient attacks of paroxysmal tachycardia are more serious, because of greater associated cardiac embarrassment. Actual cardiac decompensation at the time of operation, of course, increases the

risk considerably, although it is rarely necessary or advisable to carry out operative procedures when the heart is failing. It is still not definitely established whether digitalis and quinidine are of any value in the treatment of cardiac irregularities accompanying toxic goiter. Plummer still insists that digitalis is harmful and others, that it is a great help. We do not use digitalis in toxic goiter even in the presence of auricular fibrillation, because it has seemed to do no good and in some instances to embarrass rather than aid the heart. This applies particularly to the immediate postoperative period, during which some surgeons use it routinely for marked tachycardia with or without the presence of auricular fibrillation.

Tetany and Paralysis of the Vocal Cords. In the immediate postoperative period it is necessary to be on the watch for tetany and paralysis of the vocal cords. Tetany is comparatively rare and usually becomes evident on the second or third day after operation. When properly treated it is never fatal. It is rarely necessary to use the parathyroid hormone, calcium by mouth usually being sufficient. If an emergency arises, it can be controlled by injection of calcium intravenously. The main thing is to be constantly on the watch for tetany. Its incidence bears a direct relation to the extent of the surgical procedures, being more common in the more extensive operations. Since tetany is one of the most serious complications because it is usually permanent and there is no preparation of the parathyroid hormone which works indefinitely, we are skeptical about the wisdom of performing so-called total thyroidectomies which have been advocated by a few surgeons.

Paralysis of the vocal cords is fairly common and its incidence (from 5 to 15 per cent) appears to be related to the skill of the surgeon. In most instances it is unilateral but in rare instances is bilateral. In about half of the cases the paralysis is evident as soon as the patient awakes from the anesthetic, but in the other half does not become evident for from 12 to 36 hours after operation. It is usually associated with edema of the larynx which makes breathing difficult for from two to four days. This difficulty is relieved by inhalations of compound tincture of benzoin and a tracheotomy is almost never necessary even in patients with paralysis of both cords. It is most unusual for a vocal cord paralysis to be the cause of death following operation, although, by the increased muscular effort in breathing and the interference with sleep which it causes, the recovery of a very sick patient may be delayed.

It is of interest to see how the application of the principles outlined has affected the mortality from thyrotoxicosis in a large municipal hospital. Through the cooperation of Dr Frederick Tice and other members of the staff, it has been possible to make a study of the disease at the Cook County Hospital in Chicago. Among the cases followed by other observers the mortality from thyroidectomies for exophthalmic goiter between the years 1931 and 1933 varied from 12.7 to 13.3 per cent, with an average mortality of 13.1 per cent (total of 305 cases). The mortality from toxic adenoma

during the same period varied from 8.1 to 12.1 per cent with an average mortality of 9.8 per cent (total of 102 cases). The average mortality for non-toxic adenoma during the same period was 4.1 per cent (106 cases) and for simple goiter, 2.6 per cent (38 cases).

In the patients with exophthalmic goiter whom we have personally followed during the period 1932-1934, the mortality has been 4.2 per cent (72 cases). The number of patients with other types of goiters is too small to base conclusions on, there having been 12 cases of toxic adenoma with no deaths and 14 cases of non-toxic adenoma with no deaths. It may be seen that the mortality among the patients with exophthalmic goiter that we have followed is the same as that in the group of patients with non-toxic goiter followed by other observers. The reduction in the operative mortality in exophthalmic goiter has been accomplished without any change in surgical personnel and without any significant change in surgical technic. In interpreting these data it must be borne in mind that the operative mortality in large municipal hospitals where all general surgeons of varying skill do goiter surgery can probably never be reduced to the level reported from highly specialized private clinics where only two or three men of unusual skill do all the thyroid surgery. Our mortality is still much too high and we hope to reduce it further, but at the present time it is probably as low as in any large city hospital and lower than in many of them.

This brings up the question of specialization in goiter surgery. In the training ordinarily considered adequate to prepare a man to do general surgery, so few goiter operations are performed that sufficient opportunity is not provided for the development of surgical judgment and skill. If institutions wish to reduce their goiter mortality to the lowest possible rate, they must be prepared to have all of their thyroid surgery done by only a few men who by experience have learned to appreciate the importance of adequate preoperative preparation of their patients and have developed speed and gentleness in their surgical technic.

It is of some interest to review briefly the case histories of the patients who died in order to consider how their lives might possibly have been spared. In the first patient the basal metabolism dropped from about plus 50 per cent to about plus 25 per cent during the administration of iodine although he did not gain any weight. The preoperative course of the disease was complicated by an upper respiratory infection which it was thought, however, had cleared up at the time of operation. The disease did not appear to be particularly severe. He seemed nervous as soon as he awoke from the anesthetic and his pulse rate for the most part was 140 or over thereafter. His temperature gradually rose to 105 just before death. It was possible to detect bronchopneumonia on physical examination 13 hours before death, which occurred 60 hours after operation. In the second patient the disease was complicated by diabetes. Although the metabolism was not very high (from plus 30 to plus 40 per cent), it did not show

any reduction during the administration of iodine. His preoperative course was also characterized by frequent attacks of diarrhea and a loss of 14 pounds in weight, caused by inability to get him to cooperate enough to eat the food ordered. He created the impression of being unable to stand much and his fellow patients had predicted that he would not survive the operation. Following the thyroidectomy he had a rather stormy course with a marked tachycardia and several insulin reactions. He appeared, however, to be doing fairly well three to four days after operation, only to become worse in association with the development of lobar pneumonia from which he died five days after operation. The third patient entered the Cook County Hospital August 1, 1933. Although his basal metabolism was only about plus 40 per cent, emotional instability and muscular weakness were well marked. During the administration of iodine his metabolism, instead of dropping, rose to about plus 58 per cent and the manifestations of the disease became more marked. It was felt that he could not stand a hemithyroidectomy and, against our advice, both superior poles were ligated September 11. Following operation his metabolism did not drop but he did lose five pounds. The inferior poles were ligated against our advice October 7. Again, his basal metabolism did not drop but he did lose another nine pounds and developed a paralysis of the left vocal cord. Iodine was omitted November 5, following which his metabolism rose to plus 70 per cent. He was sent home November 26 and reentered the hospital January 3, 1934. When iodine was readministered his metabolism dropped only slightly to plus 60 per cent, but he did gain 13 pounds. A left hemithyroidectomy was done March 13, but it was greatly prolonged by the technical difficulty caused by the scar tissue from the first operations. His pulse rate rose from 110 to 160 during operation and remained at this level until three hours after operation when it became too weak to count. His temperature gradually rose to 103 and his respirations to 40. He became irrational six hours after operation and died an hour later.

In the first patient it is possible that operation was performed too soon after the upper respiratory infection. The second and third patients were not suitable risks for operation and it should either have been postponed still longer or an attempt made to reduce the intensity of the disease with roentgen-ray treatment before proceeding with surgery. The technical difficulties of operation contributed perhaps to the death of the third patient, but in these two deaths we ourselves must bear a large share of the responsibility, while in the death of the first patient the exact cause is uncertain. These deaths illustrate the main point, namely that operative mortality depends in large measure on the condition of the patient at the time of operation. The patient's life is saved in the preoperative period and very little can be done to avoid a fatal outcome after operative procedures have already been carried out. Success in the treatment depends upon intelligent co-operation between physician and surgeon.

SUMMARY

The two most important factors in determining the risk of thyroidectomy for exophthalmic goiter are the preoperative condition of the patient and the skill of the surgeon. In preparing patients for operation great attention must be paid not only to the administration of iodine but also to the administration of a diet sufficiently high in calories to make the patients gain weight, to the control of emotional instability and to rest. The severity of the postoperative reaction appears to be related more directly to emotional instability than to any other factor. There should be no hesitation about postponing operation until the condition of the patient appears satisfactory.

Selection of the time of operation is more important than the selection of the type of operation, although the thyroidectomy should be performed in at least two stages in all patients in whom there is any doubt about the ability to withstand operative procedures. Ligations of arteries do not appear to affect the intensity of the disease.

Success in the treatment depends upon intelligent cooperation between physician and surgeon. Miracles can not be performed in the postoperative period and the time to prevent postoperative crises is in the preoperative period.

By applying the principles outlined to the preoperative treatment of exophthalmic goiter at the Cook County Hospital in Chicago it has been possible to reduce the operative mortality from 13 per cent to about 4 per cent without any change in surgical personnel or surgical technic.

In order to keep the operative mortality at the lowest possible rate, hospitals should not only pay more attention to the preparation of such patients for operation, but should relegate their thyroidectomies to a few surgeons who have developed good judgment, speed and gentleness and not to general surgeons who have had little opportunity to perfect the technic of thyroid surgery or to learn contraindications to operation.

We are greatly indebted to Dr. Frederick Tice and other members of the staff of Cook County Hospital for the privilege of making many of the observations referred to.

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THE ALTERNATIVE TO REVOLUTION *

By GLENN FRANK, *Madison, Wisconsin*

THE air is, at the moment, filled with premonitions of profound change in the political, social, and economic life of the United States

Many Americans are sincerely fearful that we may rush into changes that will bring our traditional order of private enterprise and political liberty to a decisive and disastrous end. And they see no matured alternative around which grave doubts do not swarm. These Americans have no personal or political axes to grind by the expression of this fear. Their concern is genuine.

A few Americans, without this sincerity of concern, are attempting to further personal and partisan interests by branding even the simplest and most obviously sensible suggestion of change as part of a sinister plot to communize the nation. Save to express my contempt for such tactics, I shall waste no words on these ventures in shoddy politics and sordid economic propaganda. Sooner or later, the bogey-monger, whether hailing from the ranks of radicalism or reaction, is strangled by his own insincerity.

But, whether sobered by calm analysis or stimulated by faked alarms, the national mind is anxiously speculating on the turn affairs may take in the days ahead. Can we ride the storm without basic changes in the traditional order of American life and enterprise or are we in for a drastic reordering of our political and economic arrangements? I want to air this issue with as much candor and realism as I can muster.

No simple and single answer to this question is possible. The forces of change now in operation may be dammed up by inflexible tradition until they break the dykes with a rush of revolutionary energy or they may be directed by flexible intelligence into a process of social reconstruction that will give fresh significance and assured stability to our national future. Because I believe that the future and fortune of all of us now living will be determined by the outcome of the battle royal that is now on between the forces of inflexible tradition and the forces of flexible intelligence, I have chosen to chart the issues of this battle in terms of the current national situation.

I am convinced that profound historic change impends in the life and enterprise of our time. I am not at all sure of the direction this change will take. We may be in for a long retrogression or we may be on the threshold of renaissance. The blackening of the skies that began in 1929 may have heralded a permanent eclipse of the national genius or these may be but the grey hours before a social sunrise that will warm and illumine our lives where transient disaster has chilled and darkened them. In either case, the America of tomorrow will, I am convinced, be radically different from the

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America of yesterday's textbook or of today's newspaper. And what that America will be like will depend primarily upon whether the forces of inflexible tradition or the forces of flexible intelligence direct our affairs in the days immediately ahead.

Our national life is just now in the fourth phase of a sequence of events that has before in history brought whole peoples to the social crossroads where decisions affecting their destiny have had to be made. Unless I grossly misread the meaning of the last two decades of American history, four distinct developments have brought the American social order to its present critical juncture.

First, old philosophies and old procedures which had long dominated our political, social, and economic life fell into varying degrees of futility through the failures of American leaderships to keep them progressively adjusted to the new circumstances of this new age of science, technology, and plenty.

Second, while these old philosophies and old procedures were falling into futility, new philosophies and new procedures, more alert to the needs and better adapted to the nature of this new age, were being patiently and unobtrusively elaborated by scientists and seers whose historic mission it is to be the unofficial statesmen who, in freedom from the clamor of constituencies and the compulsions to compromise blaze new trails of thought and action which the official statesmen may later follow if they will.

Third, a long period of manifest maladjustment between the old policies and the new problems of American life ensued, but, despite the heavy hand this maladjustment laid upon the lives of men, the masses of Americans clung uncritically to the doctrines of the fathers in matters political and economic.

Fourth, in the wake of the world-wide economic collapse, from one end of the United States to the other, men have been shaken out of the sterile serenity that marked their mood in the days of the pathological prosperity of the Coolidge era, with the result that today they no longer display reluctance to question even the major assumptions upon which their life and enterprise have long been organized.

It is the mood of this fourth phase that makes critical the present juncture in American affairs. The present temper of the American mind differs vividly from its pre-depression temper. In the days of our phantom prosperity we were sleek and self-satisfied. We were well-fed and wanted nothing so much as to be let alone. We were impatient of those queer persons who were forever raising disturbing questions about our political, social, and economic policies. As if anything could possibly be wrong with a civilization that was paying such excellent dividends! The result was that, throughout the prosperity period, we turned deaf ears to the advocates of political, social, and economic readjustments that might well have averted the disaster that has darkened our lives since 1929.

Even I, mild and modest commentator that I am, found myself damned as a dangerous citizen by certain Wisconsin politicians and a few Wisconsin industrialists, during the 1932 campaign, for having advocated ideas which have since been hailed as the soundest of sound business sense by that notoriously red organization, the United States Chamber of Commerce.

As long as the nation was on its economic joy ride, new ideas had hard sledding. Almost the sole exception to this was the lush growth of bootleg religions and the rise of an apostolate of fakirs who led thousands of otherwise intelligent Americans to believe that, in their wistful quest for the deeper meaning of existence, they could suck the juices of a living gospel from the dead rinds of ancient superstitions or the green stalks of bogus psychologies. It may be that mankind will always rebel in this irrational sort of way against an era that becomes so exclusively absorbed in the goods and chattels of a crass prosperity. At any rate, aside from this single exception of the gullible embracement of improvised religions, the American mind betrayed a baffling immunity to new ideas as long as the economic skies were bright. Until the chill and shadow of the market collapse fell upon us, we were smug to the point of blindness to the basic drift of our civilization. It would be difficult, I think, to put one's finger upon even a single truly productive new idea in politics or economics which swept the mass mind while the phase of prosperity was on.

An old Scotchman, seeking to account for this seeming immunity of the American mind to new ideas, said, "The heather was wet!" And anyone who has tramped over the hills of Scotland knows that when the heather is wet fires do not sweep easily across the fields. But today the situation is the exact reverse. The heather is not wet today. The heather is dry! Disillusionment has done its perfect work. The man in the street, along with the man in the furrow, is straining at the leash of old dogmas of politics and economics that have failed to keep hunger from his stomach, cold from his body, and fear from his heart. The tethers of a thousand traditional loyalties have slipped during the last five years as men have watched the very ground stakes of their social order loosen. And from one end of the United States to the other men are today fumbling blindly for some lead out of the blind alleys into which blind leaderships led them.

Such a mood is at once a grave danger and a great opportunity. A grave danger if irresponsible demagoguery dominates it! A great opportunity if responsible statesmanship directs it!

In its present mood the mass mind is willing to follow responsible statesmanship. It would prefer to follow responsible statesmanship. It may follow irresponsible demagoguery. And it lies wholly with statesmanship to say which turn affairs shall take.

The American mind, unless I grossly misread its present mood, will take counsel of its patience while a Roosevelt gathers power unprecedented into his hands and cuts the red tape that normally binds government to the hitching post of inaction. But it will not unduly prolong its patience. There is a latent impatience moving restlessly close under the surface of the liberal patience Americans generally have displayed during the difficult days of the last five years. The mass mind expects constructive action and creative results to follow the freedom to act which its mood made Congress make possible something more than a year ago.

And—let us speak plainly—the mass mind expects something more than a Red Cross statesmanship that momentarily salves the economic wounds of the time and subsidizes into transient silence a growing army of the legitimately discontented. It expects careful but courageous readjustments of our political, social, and economic policies that will enable us to take full advantage of the fruits of this new age of science, technology, and plenty.

It was for this, and this alone, that we adjourned so much that is traditional in our democracy. It was for this, and this alone, that we set up a crisis government under which a Roosevelt is given in peace time powers far beyond the powers given to a Wilson in war time. And the mass mind will hold this crisis government to strict accountability. If the fruits of this freedom to act, which the mass mood made possible, should fail visibly to ripen, the mass mind will turn inevitably to an alternative leadership. And the danger is that it might be none too discriminating in its selection of the alternative.

One thing should by now be clear, alike to the Roosevelt administration and to the political opposition, and that is this. We are past the point at which beating the tom-tom for obsolete traditions of politics and economics can either satisfy the mass mind or bring recovery and stabilization to our national life.

We still have time to choose between guided reconstruction and unguided revolt!

I use the word "revolt" instead of the word "revolution" because there is a basic difference between the two. This distinction was dramatized by the Duc de la Rochefoucauld as he stood with King Louis watching the Parisian mob storm the Bastille in 1789.

"This is revolt," cried Louis.

"No, Sire," said Rochefoucauld, "it is revolution."

Revolt was there, of course, but Rochefoucauld was right in reminding Louis that he was watching the profounder process of revolution in which his people had set deliberately out to readjust the old tools of government, which were obsolete, to the new tasks of government, which were obvious. And this, as Rochefoucauld saw, was a more fundamental thing than mere revolt. It was a far-reaching process of social readjustment in which revolt was but an incident that might or might not take place.

There can be revolt without revolution. There can be revolution without revolt. In fact, the greatest revolutions are not marred by revolts. We do not want revolt in the United States. And, unless the American intelligence wholly abdicates, we can face difficulties far more drastic than we have yet known without revolt. But, unless we are willing to run the risk of a lapse into complete social and economic chaos, we cannot avoid revolution, if by revolution we mean what we should mean, namely, evolution under the guidance of an intelligence that is neither enslaved by inflexible tradition nor dragged at the heels of ill-conceived change.

Changes are forever taking place in the life and enterprise of living

peoples When change stops we may know that the genius of a people has gone cold and a civilization has died We cannot escape the fact of change, no matter how stubborn our orthodoxies The problem is not to prevent change but to pilot it to productive ends

If flexible intelligence were always at the helm, we would keep our social institutions progressively adjusted to the changing circumstances that are inseparable from a living civilization And the result would be that society would never come to dramatic turns in the road where it had to undertake wholesale readjustments of its policies to situations leadership had too long neglected But, unhappily, this is not the way the race has functioned to date There is always a lag between the swiftly changing life and the slowly changing institutions of a people And it is this fact of lag that gives rise to the sort of crisis that has frozen the fountains of our enterprise for the last five years

It is right that there should be some lag Otherwise our institutions would be in a continuous St Vitus dance of change that would make ordered life and productive enterprise impossible We do not want our institutions to chase down the street after every Pied Piper who has snared a new notion from the cloudland of theory Most new ideas are wrong By which I mean that the race is lucky if experience ratifies as true one out of every thousand new theories it evolves Most of the ideas that have survived the stress and storm of the centuries are right I mean the ideas that have survived with vitality, not the ideas that have merely stayed on as cadavers to poison the intellectual atmosphere All of which means that we must build our lives, individual and institutional, mainly on ideas the race has hammered out on the anvil of experience No generation can expect to add more than a little to the wisdom of its ancestors

It is not a matter of deciding whether we shall cling to tradition or cultivate change Tradition and change are not alternatives They are two indispensable elements of civilization that must be kept in the proper relation

A certain amount of social lag is desirable in the interest of continuity and stability We want our institutions to maintain a saving continuity We do not want our churches, schools, and economic establishments taken to pieces every evening at sundown and put together again in some new pattern every morning at sunup But we must remember that our institutions must maintain continuity with the future as well as continuity with the past Otherwise they will some day find themselves tenantless and dark in the midst of a generation whose allegiance they no longer command We want our institutions to have stability But their stability must be the equilibrium of steadied action not of mere inertia Otherwise they become but so much waste lumber cluttering the current scene A certain degree of lag between institutional change and social change is, therefore, necessary if civilization is to be kept a going concern

If, however, we permit the policies and procedures of our institutions, under the lordship of inflexible tradition, to lag too far behind the changes that are taking place in the society they were designed to serve, glaring maladjustments occur. These maladjustments produce a social instability. And this social instability may at any moment lead an otherwise patient people blindly to break continuity with the sound as well as the unsound values of the past.

This, I fear, is the pass to which we have permitted American affairs to come!

I have not come to this conclusion from reading the inflammatory manifestos of radical agitators. I have been driven to this conviction by such eminently respectable documents as the report of former President Hoover's Research Committee on Recent Social Trends. It is, I submit, impossible for any literate American to read the two major volumes of this Hoover report, together with the subsidiary volumes that elaborate its findings, without realizing that our American civilization has become, both in its nature and in its needs, a radically different civilization from the American civilization in terms of which our forefathers determined the major patterns and designed the major institutions of our political, social, and economic life. The resistless forces of physical science and industrial technology have completely remade the civilization going on outside the walls of our institutions. The problems that this changed and changing civilization is today putting to government, to business, to industry, to finance, to the church, to the school, and to the family, as these problems are assembled and analyzed in this Hoover report, are drastically different from the problems that faced us even a generation ago.

And the report of this Hoover committee dramatizes, as no document before or since has dramatized, the fatal lag between our old policies and our new problems. This monumental research in social trends boils down to this: most of the major patterns and most of the major institutions of our political, social, and economic life were designed in terms of an American civilization in which (1) the scale of enterprise was small, (2) the relationships of life simple, and (3) the tempo of affairs slow. But now these institutions must function in and serve an American civilization (1) in which the scale of enterprise is no longer small, but vast, (2) in which the relationships of life are no longer simple, but complex, and (3) in which the tempo of affairs is no longer slow, but swift.

The overshadowing problem of this generation is to keep the response of our institutions to the sort of sweeping changes reflected in this Hoover report a guided reconstruction without revolt. And I submit that nothing save a flexible intelligence, mediating wisely between the forces of tradition and the forces of change, can possibly insure this result.

I give you two immortal pronouncements, rich in statesmanlike guidance to a people, like ourselves, caught in the swirl of a rapidly changing civilization—one from John Stuart Mill, the other from Viscount Morley

"The future of mankind will be gravely imperiled," said John Stuart Mill, "if great questions are left to be fought out between ignorant change and ignorant opposition to change"

This sentence might with profit be printed on the title pages of the 1936 campaign textbooks of both the Republican and Democratic parties!

"Great economic and social forces flow with tidal sweep over communities only half conscious of that which is befalling them," said Viscount Morley "Wise statesmen are those who foresee what time is thus bringing, and try to shape institutions and to mould men's thought and purpose in accordance with the change that is silently surrounding them"

It is this emancipation from inflexible tradition and this exercise of flexible intelligence, expressed and exemplified by the John Stuart Mills and the Viscount Morleys, that constitutes the most crying need of this distraught time It is this sort of judgment and action that the schools, colleges, and universities must prepare men to bring to those readjustments that have become imperative as a result of the silent but sweeping revolution that science and technology are working in the political, social, and economic arrangements of American life

The question is not what we should think about some hypothetical "revolt" that the bogey-makers picture as stealing upon us unawares, like a thief in the night, hidden in the cloak of some professor who has had the insight to see and the courage to say that American capitalism must effect a sounder distribution of buying power if it wants to survive, or lurking in the surplice of some clergyman who has come to suspect that maybe war after all is not the whole will of God

The question is what we purpose to do about the actual "revolution" through which the United States is now passing, the revolution induced by physical science and industrial technology, the revolution so adequately reported and ably documented by the Hoover Research Committee on Recent Social Trends

It is no easy matter to bring flexible intelligence to bear upon public affairs in so confused a time A thousand pressures—political, social, professional, and economic—come continually upon us to spend our energies fighting the windmills of imaginary threats of revolt instead of bringing our intelligence carefully but courageously to bear upon that guided reconstruction of American life which is, in my judgment, the only alternative to the increasing insecurity and ultimate collapse of our social and economic orders

There are frightened reactionaries who are sure we are drifting into Communism There are frightened radicals who are sure we are drifting into Fascism We may, I think, take both these fears with a grain of salt Nations never *drift* into either Fascism or Communism Nations go Fascist or Communist only when the soil is thoroughly prepared for the seed and when there is behind the Fascist or Communist push a capable, clear-headed, closely knit, and rigidly disciplined group able to get its hands quickly on

the levers of military and economic power. There is nothing in the American picture to indicate that we have reached such a point. And there is nothing inherent in the situation that need ever lead us to such a pass.

We are not an easily inflammable people. Even the more moderate movement of American Socialism has not made dramatic headway during the last decade. In 1920, Eugene Debs polled more than 200,000 votes in New York State and more than 900,000 votes in the country as a whole. Twelve years later, in 1932, in a time of incredible economic hardship, when the wine of discontent was everywhere in ferment, the able and persuasive Norman Thomas polled only 175,000 votes in New York State and only about 800,000 votes in the country as a whole.

I am aware that, in 1932, a large protest vote, that might under more normal circumstances have gone to the Socialist candidate, went to Franklin D. Roosevelt. But that hardly argued the imminence of rebellion, for what has seemed to some the radicalism of Rooseveltian policies has come into the picture since the election. I submit, therefore, that both the low vote of Norman Thomas and the high vote of Franklin D. Roosevelt indicate that we are not an easily inflammable people. And, for this reason, I refuse to be stampeded by the alarmists.

I believe that the American tradition of private enterprise and political liberty, if now corrected in the light of experience and wisely adjusted to the new requirements of an age of plenty, will be in the forefront after all of us now living have long been dead and the Fascisms and Communisms of the moment have become the relics of dead yesterdays. I hope you did not overlook the "if" clause in that sentence, for candor compels me to say that I could not so confidently predict the survival of capitalism and democracy unless I made the prediction contingent upon our willingness to face fresh problems with fresh minds and to rethink and recast our basic policies respecting wages, hours, prices, profits, and control, as well as the processes of democratic self-government, in the light of the new circumstances of this new age of science, technology, and plenty.

The blunt truth is that the fate alike of private enterprise and of political liberty is wholly dependent upon the flexibility of intelligence we can muster in the decade immediately before us. There is no area of our common life—whether it be politics, economics, or religion—in which the current situation does not cry aloud for flexible intelligence.

Certainly flexible intelligence is needed in the field of politics. Political action has lately assumed a new importance for the American future. Donn Byrne, weaver of colorful tales of his beloved Ulster, once wrote, "I have never seen a government that brought heavier apples to the trees or heavier salmon to the rivers or a more purple heather and for this reason politics means nothing to me." Strange doctrine for an Irishman! It was doubtless temperament that led this Celtic prose-poet to assume so cavalier an attitude toward politics. It must be admitted, however, that, until lately, signs were not wanting that we might be passing out of the age of politics,

in the old sense of politics. The tone and temper, if not indeed the very structure, of our society were increasingly determined by non-political forces. Forces of physical science! Forces of industrial technology! Forces of cultural reevaluation! These, rather than the decisions of politicians, were the forces that, for half a century, had been making, unmaking, and remaking civilizations throughout the Western world. And yet, at the moment, American destiny is, I am convinced, strangely dependent upon the quality of political thought and action we can contrive to bring to the direction of our industrial and international affairs in the days ahead.

We cannot expect more than transient and insecure phases of recovery until, as I have suggested, we have rethought and recast our basic policies respecting wages, hours, prices, profits, and control in terms of the new circumstances of this new age of science, technology, and plenty, and until we have achieved a rationalized program of world relations. I have been driven reluctantly to the conclusion that, as American life is now organized, we shall not find in the ranks of business, industry, and finance a leadership that can effect promptly enough and apply widely enough those basic readjustments of economic policy that events are forcing upon us as the price of recovery and stabilization, and that, for the time being at least, the initiative for these readjustments must come from political leadership despite the dangers inherent in any undue extension of political sovereignty over private enterprise.

It is, I suspect, a flexibly intelligent political leadership, and it alone, that can break the impasse to which the forces of science and technology, in stubborn conflict with obsolete political and economic policies, have brought the American social order.

Certainly flexible intelligence is needed in the field of economics. I am singularly unmoved by the wolf cries of the Dr. Wirts who see a bolshevik behind every bush. But I am not blind to the fact that the fate of private initiative is definitely at stake in the whirl of affairs at Washington today. Individualism, rugged and otherwise, is on the run. This throws an unprecedented challenge to the sincere friends of private initiative. I count myself among the friends of private initiative.

I am not at all enamored of the prospect of having my own and the nation's life ordered about by bureaucrats. I should be reluctant to see the intricate processes of the nation's economic enterprise put at the mercy of the quality of intelligence that American politics has, by and large, been able to recruit during the last quarter century. I do not believe that the complex economic life of the United States can ever be run effectively from Washington. I doubt the wisdom of having political persons dictate in detail the risks and routines of American business and industry. And this doubt survives even the muddling mismanagement of the nation's enterprise by many of the leaders of business, industry, and finance in the decade before 1929.

But I am, I hope, a realist. And I set it down as a deep conviction that a sustained study of the passing show has forced upon me that if the freedom of private initiative dies on this continent in the next ten years its friends will have been responsible for its death because they failed to bring a flexible intelligence to its operation in the last ten years. For the last ten years, private initiative has been doing its level best to commit suicide. Under such circumstances, the more a statesman believed in private initiative, the more he would be moved to grab private initiative by the collar and seek to discipline it before it took the last fatal leap.

There is no dominant body of either Fascist or Communist thought in the United States. Franklin D. Roosevelt does not want to be a dictator. But neither an intelligent president nor an impatient people will stand idly by and see a whole civilization sink just in order to preserve the dogma of private initiative.

It lies, I think, with the leadership of American business, industry, and finance to say just how far infringements on private initiative shall permanently go in the readjustments imperatively before us. If the leadership of American industry will now pool its varied genius in a nationally integrated effort to work out and to put into effect as promptly as possible wage, hour, price, and profit policies that will spread the normal national income widely enough to make the toiling millions a dependable consumer market for the maximum output of our machine economy, if the leadership of American industry will make the increase, the enrichment, and the stabilization of life for the millions its first obligation, and if the leadership of American industry will expect private profit to come, as I think private profit should come, only as a by-product of and compensation for its statesmanlike administration of the social function of industry, neither the President nor the Congress will spend much time trying to fasten any dictatorship on American industry. And, incidentally, industrialists will find the size and the security of their total profits increased, even if the profit margin on the individual article or action is narrowed. If the leadership of American finance will produce a banking system that will serve instead of sink the nation's enterprises, no one will lie awake nights to devise halts and hobbles for bankers.

Nearly everybody in America prefers private initiative—if it will only deliver the goods. The economic disaster that has befallen us is not, in my judgment, inherent in the nature of private initiative, but is the result of its gross mismanagement. The preservation of private initiative will depend wholly, I think, upon its practitioners' bringing flexible intelligence to its operation in this new age of science, technology, and plenty.

Certainly flexible intelligence is needed in the field of religion if we are to preserve, as a sweetening and savoring factor in our national life, certain priceless values that are gravely endangered in this phase of social disillusionment. It may seem to some beside the point to inject the problem

of religion into this study of the social and economic renewal of American life. Let me tell you why I think it is not.

Despite the protestations of a few disgruntled politicians and short-sighted business men, the old order of catch-as-catch-can politics and economics is as dead as the dodo. The traditional order of American life and enterprise has come definitely to a cross roads where we must decide between a voluntary cooperation of all classes for common ends and submission to a regime of compulsion that will impose upon us political and economic arrangements that will break the stalemate of the last five years.

No authentic American wants to see compulsion come. The essence of the American spirit is its love of freedom. But there are only two regimes under which free men can survive: (1) the virtual anarchy of *laissez faire*, or (2) control through wide and willing cooperation. In a simple society *laissez faire* works well and free men enjoy stretching their powers unhindered. In a complex society *laissez faire* does not work well and sooner or later free men find their freedom worthless in the midst of a crashing collapse of their economic order.

Having practiced the virtual anarchy of *laissez faire* so long, free men, when caught in a collapse like the crash of 1929, rush distractedly about with next to no disciplined capacity for that prompt cooperation for common ends which the enterprise of recovery and stabilization requires. And, in their distraction, they all too often fall wistfully into the arms of dictatorship. This is the story of Italy. This is the story of Russia. This is the story of Germany. This may become the story of France. This may happen in England. Will this be the story in the United States? It may!

There is just one thing that will prevent our surrender to an increasing compulsion. And that is a nation-wide crusade, essentially religious in its passion and purpose, for the universal cooperation of individuals, groups, and classes in the determination of policy in terms of the common welfare of the whole nation. The total combined forces of Catholicism and Protestantism, augmented by all the anonymous religious concern that may reside in our people, should now be brought to focus on the stimulation of a vigorous faith in and active effort toward a nation-wide reconsideration and redirection of our political, social, and economic orders through a vast popular cooperation in which personal and class interests are adjourned and the increase, enrichment, and stabilization of life for the millions made the dominant concern.

Until the economics of a New Deal are fortified by the religion of a New Deal, we shall continue to be victimized by the predatory trickeries of the trader and the polite treasuries of the politician. And this social passion for the common welfare of the nation must be more than a crusade for secular uplift. It must sink its roots in the soil of a faith that lies beyond economics. The future of American religion and the future of the Ameri-

can social order are more intimately interlocked than many, in the facile modernism of their reasoning, have been inclined to think

It is disclosing no secret to say that the fountains of religious concern have tended to go dry while for the last half century we have wandered in the far country of materialism, concentrating our energies upon laying the physical foundations and elaborating the instruments of our machine economy which today stands stalled in our presence

Many are rightly concerned over the widespread secession from belief in God that has been increasingly evident as the machine age has come to maturity I know the barbarisms and indignities that fanatics have perpetrated in the name of God I know the innumerable caricatures that shortsighted men have drawn of His countenance, reading their own lusts and limitations into His purposes I know how often whole peoples have projected either the tyranny or the tenderness of their social orders into their concept of God I know how often sinister interests have sought to use God as a smoke screen for their anti-social adventures But I know also the myriad army of saints and seers whose lives, illuminated by the light of His countenance, have been given to fertilize the soil from which the freedom, as well as the faith, of the race has flowered And I am convinced that a civilization that exiles an exalted concept of God from its heart dries up one of the major well-springs of its power

I agree with the sometimes exquisitely pagan Edna St Vincent Millay when she writes

Not Truth, but Faith, it is
That keeps the world alive If all at once
Faith were to slacken—that unconscious Faith
Which must, I know, yet be the corner stone
Of all believing—birds now flying fearless
Across would drop in terror to the earth,
Fishes would drown, and the all-governing rems
Would tangle in the frantic hands of God
And the worlds gallop headlong to destruction

Remote as their relation may seem to the practicalities of social and economic renewal, here are questions quite as vital to the national future as industrial codes and tariff agreements How shall the forces of religion make God again believable to men who have lost all faith in any lordship of life? How shall we save men of this generation from a corrosive cynicism? How shall we help disillusioned men to recapture a courageous confidence that life is not just a blind dance of atoms, but a meaningful adventure worthy of deathless objectives?

I shall not presume to make any final answer to these questions that have harrassed mankind since the infancy of the race But of one thing I feel sure few, if any, men are drawn to belief or driven into disbelief in God by the traditional dialectics of the theists and atheists Men's belief in God is broken or buttressed less by the arguments they hear than by the

way in which the social order, in which they have to live, breaks or buttresses their lives

A man whose life has been broken by the brutality of his fellows is less likely to believe in a beneficent God "Friends should be kind to a despairing man," Job is found to say in one of the modern translations of the Old Testament, "or he will give up faith in the Almighty" And Johan Bojer, in his "The Great Hunger," makes an old Norwegian farmer say, "I sowed my enemy's field with corn in order that God might continue to exist" And, from an ancient scripture and a modern tale, I bring you the conviction that men's belief or disbelief in God may be but a reflection of what society has done to their lives If we compel a man to live his life in a social order bereft of love and its sterner counterpart, justice, we must not be surprised if he has difficulty in believing in a God of love and justice We cannot expect a God of love to be wholly convincing in a loveless world And to ask men to believe in a God of justice when their whole lives have been blighted by injustice is, to say the least, optimistic

Men of flexible intelligence, concerned to renew and release the religious impulse as a factor in the reinvigoration of our national life, will not attempt to combat atheism or to cultivate a belief in God by sheer dialectics For men of flexible intelligence will know that the future of religion on this continent depends less upon the explanations of professors and the exhortations of parsons than upon the kind of social order we build on this continent

All of which means that, if the future of the social order is influenced by the quality of religion, the future of religion is also influenced by the quality of the social order If we are to achieve a balanced and meaningful civilization, therefore, we must work concurrently for the revitalization of religion and the reconstruction of the social order

And now my argument draws to a close I have exalted the virtue of flexible intelligence as the one hope of a stable and significant national future It remains only for me to say that, in my judgment, the stimulation and discipline of this flexible intelligence is the supreme contribution the schools, colleges, and universities can make to this disordered and distraught time Need I say that schools, colleges, and universities cannot stimulate and discipline this flexible intelligence unless they are themselves left free to bring flexible intelligence to bear upon the problems with which they must deal? Yes, I think it must be said, for we may be running into a time in which greater pressures than ever before will be brought to bear upon the schools, colleges, and universities to mould them to a pattern, to soft-pedal their researches into living realities, to tell them what they may and may not say

There are three major systems of political control now functioning in the Western world—Fascism, Communism, and Democracy Fascism and Communism have decided what they will do with their schools They have decided that the laboratory must take orders from the legislature There

are no dissenting professors in Italy. Dissenters have either suffered exile or bought their posts at the price of silence. There are no dissenting professors in Moscow. They are either nursing their wounds in Paris or picking up a precarious living as best they can elsewhere in the Western world. And now Hitler has put the sign of the Swastika on German scholarship. As Charles E. Merriam has suggested, it remains only for the democracies of the West to say that they will not tolerate differences of opinion to make it unanimous, and then we can blow out the light and fight it out in the dark, for, when the cry of intelligence is silenced, the rattle of machine guns begins.

EDITORIALS

CONTROL OF MEDICAL PRACTICE

Fairness, it would seem, demands, in any human transaction, that the rights of all parties shall receive due consideration. This principle should apply to the doctor-patient relationship, which is in effect the sale (when it isn't a gift) of medical care to the patient by the doctor. Both parties to the transaction are deeply interested. To the patient, it may be a life or death matter, to the doctor, a portion of his livelihood. Exploitation of either by the other is incompatible with sound ethics. Yet we have it on high authority that "all features of medical service in any method of medical practice should be under the control of the medical profession. No other body or individual is legally or educationally equipped to exercise such control." The patient is to take what he can get and be thankful. So-called organized medicine, an interested party, is to be the sole arbiter of how the public, the other interested party, can obtain its medical service. The public is to have no voice in the matter. The medical profession does not admit that anyone can tell it anything about these matters. Such an attitude by "organized medicine" is explicable only on the theory that the fear of state medicine has given it the jitters.

The statement that none is equipped educationally or legally to exercise control over medical service save the doctor will have to be supported by evidence. One might even question whether the doctor himself is fully equipped. What, for example, does he know in any expert way of the economic and social factors that enter into so complex a problem as the rendering of adequate medical care to the whole community? How much does he know of the prevention of disease? Precious little, and it will make a bigger hit with the public if he admits this and seeks advice, than if he assumes an attitude of omniscience. Even in the biologic aspects of his applied science, the physician leans heavily on the pure scientist, the physiologist, the biochemist, the physicist and others. Why should he not do likewise in the social? Perfection in the technic of any human enterprise is approached by the cooperation of all persons who have any intellectual contributions to make toward it. Improvement in supplying the community with medical care will be made by the collaboration of persons of varied interest, the health officer, the nurse, the social worker, the economist, the business administrator and others, as well as the man of medicine. Moreover, the public, that is to say the patient taken collectively, has a right to be heard.

Improved methods of rendering medical service, like advances in the science of medicine or any other science, will be found by experiment. Various types of medical practice, group practice, contract practice, industrial medical services, group prepayment plans, health insurance and any

others that seem to offer some promise, must be tried out. If experience shows them undesirable, they will naturally languish and die. It is to be remembered that a type of service that is suitable in one locality, or for one group of people, may be totally unsuitable for another. There must be a high degree of adaptability on the part of medicine, organized or unorganized, to meet various needs. In so far as it genuinely seeks to find better ways of furnishing medical care, it will gain public confidence. In so far as it adopts an attitude of fearsome standpattism, it will lose it. The profession ought always to remember that the doctor exists for the patient, not the patient for the doctor.

J H MEANS

AN ADVANCE IN THE DIAGNOSIS OF LEAD POISONING

The diagnosis of lead poisoning by its symptoms and by the signs found on physical examination is usually uncertain and needs for its confirmation a history of exposure to lead and the additional evidence procurable by laboratory tests. In adults the history of exposure to lead may be quite obvious as, for example, in those cases which arise among workers burning off lead paint with torches in enclosed spaces, or the determination of exposure may require considerable technical knowledge of industrial processes and not a little detective ability. The running down of the cause of a recent small epidemic in which the source of lead exposure was found to be the burning in stoves of discarded wooden battery casings impregnated with lead salts is an instance of the keenness that may be required in such an inquiry. In infants and children the patient may be able to give no assistance, and unless the physician is well aware of the frequency of lead poisoning at an early age he may not obtain from others the history of gnawing paint from window-sills or from toys, or of eating enamel flakes from cribs that would throw another light on the diagnosis of brain tumor, epilepsy, or appendicitis suggested by the symptoms.

The frequent lack of decisive symptoms, signs, or history in cases which nevertheless suggest the possibility of lead poisoning lends especial interest to any advance in the detection of lead poisoning by laboratory tests.

It was observed many years ago that the stippling of red cells exhibited a certain parallelism with the symptoms of active lead poisoning, and this simple laboratory method, that of studying the stained blood smear for stippled cells, remains one of the most valuable diagnostic measures. Stippled cells are, however, absent in as high as 30 per cent (Park) of cases of lead poisoning, and because of this inconstancy and because of a desire for a more quantitative method, the study of lead in the excreta and in the body itself has been pushed in recent years.

A primary difficulty arises from the fact that the presence of lead in the body or in the excreta proves only that exposure to lead has occurred and not that the defense mechanisms of the body have been overcome so

that active lead intoxication is in progress. Ingested lead may be held for the most part in insoluble forms in the digestive canal, and the presence of even considerable lead in the stools is not certain proof of lead absorption or intoxication. Lead excreted in the urine is, of course, derived from the lead in the blood stream and it may be assumed that its amount is usually roughly proportional to that of the circulating lead. The amount of circulating lead is undoubtedly the most important factor in determining whether or not damage to susceptible tissues will occur. The quantitative determination of lead in the urine should therefore be of great assistance in deciding the question of the presence of active lead poisoning. Certain difficulties, however, detract from the value of the method. In the first place, individuals exposed to lead may successfully store lead in their bones as rapidly as it enters their blood streams, they are instances of what might be termed compensated as opposed to active lead poisoning. The level of lead in their blood streams perhaps never reaches the height necessary to produce injury to susceptible tissues. Yet there is constantly some lead in their blood streams and constantly some lead excreted in the urine. Now the difference between the amount of urinary lead in such a case and in a case of active lead poisoning is usually less than a milligram in a 24 hour period. The necessary delicacy of chemical technic to dependably demonstrate difference of this order in the amount of urinary lead is not readily acquired. The method is valuable, therefore, when available, but for the majority of cases it is inapplicable because technical difficulties and expense have barred it from most laboratories.

The most positive evidence of active lead poisoning would evidently consist of quantitative analysis of the blood which would indicate the presence of an amount of lead incompatible with mere compensated lead poisoning. The amount of lead in the blood is too minute for present chemical methods. The application of spectographic analysis to blood ash has, however, proved fruitful (Shipley, Scott and Blumberg¹) and the results of this method so far constitute a distinct step forward. The delicacy of the method is so great that the absence of lead bands in the spectogram constitutes definite evidence of the absence of circulating lead. If lead bands are found an absolute quantitative estimation of the amount of lead present cannot be made, but there appears to be a difference in intensity which can be made use of in distinguishing between compensated and active cases of poisoning.

From a practical point of view, the new method has both difficulties and advantages. The expense of the apparatus and the necessary skill and experience for its use and for the interpretation of results will rule out the method for routine use in hospital laboratories. On the other hand, the manipulations involved in a single test are infinitely less time-consuming than are those needed for a quantitative chemical determination of lead in

¹ SHIPLEY, P. G., SCOTT, T. F. M. and BLUMBERG, H. Spectographic detection of lead in blood as aid to clinical diagnosis of plumbism, *Bull. Johns Hopkins Hosp.*, 1932, 11, 327-328.

the urine. A large city might be served by one apparatus in a central laboratory. The result may be obtained more quickly than by chemical methods, and it would appear that since the possible sources of error are less numerous the result should be more dependable. Research in the mechanisms of lead poisoning will be aided by the development of this analytic method which is applicable not only to the blood and other fluids but to the solid tissues of the body as well. Its use as an aid in the clinical diagnosis of lead poisoning will no doubt rapidly become general.

REVIEWS

A Diabetic Manual By ELLIOTT P JOSLIN Fifth Edition 224 pages, 14 × 20.5 cm Lea and Febiger, Philadelphia 1934 Price, \$2.00

This small volume is so widely known to the profession as to need only brief review. To those who have not employed it in their practice it may be highly recommended, especially for intelligent patients. It is written so as to present to the patient, and incidentally to his physician, the more important facts concerning diabetes: the factors predisposing to it, its symptoms, course, complications, prognosis, relationship to marriage and pregnancy, and the various aspects of its treatment by diet and insulin.

However, it is not only facts that Dr. Joslin presents, but a religion for the diabetic. To adhere rigorously to treatment in order to live longer is shown to be the diabetic's duty not only to himself but to other diabetics who will be encouraged to do likewise. The author's enthusiasm leads him into a peculiarly personal method of presentation. He pleads the cause of optimism for the diabetic and goes at some length into the statistical basis for optimism. Pictures of vigorous youngsters with diabetes are freely used. Short case histories are presented to illustrate the results both of good treatment and neglect of treatment. There is no other manual for diabetics which does so much to develop the morale of the patient.

M C P

Some Modern Extensions of Beaumont's Studies on Alexis St. Martin Beaumont Foundation Lectures. Reprinted from the *Journal of the Michigan State Medical Society*, March to May, 1933. By W. B. CANNON, M.D., S.D., LL.D., George Higginson Professor of Physiology, Harvard Medical School. 87 pages, 13.5 × 20.5 cm. Wayne County Medical Society, 4421 Woodward at Canfield Detroit 1933.

The Twelfth Series of Beaumont Foundation Lectures commemorated the one hundredth anniversary of the publication of William Beaumont's classic "Experiments and Observations on the Gastric Juice and the Physiology of Digestion." As lecturer, Dr. Cannon chose to compare modern knowledge of certain phases of digestive physiology with Beaumont's observations in these same fields. The three lectures deal with "Thirst and Hunger," "The Important Relations of Digestion and Health," and "Digestive Disturbances Produced by Pain and Emotional Excitement." They constitute interesting and clearly presented accounts of advances in these fields but are not complete surveys of present knowledge, and do not present any new concepts.

M C P

Practical Methods in Biochemistry By F. C. KOCH, Professor of Physiological Chemistry, University of Chicago, vii + 282 pages, 16 × 23.5 cm. William Wood and Co., Baltimore 1934. Price, \$2.25.

For some time physiological chemistry departments have found it necessary to formulate manuals of their own for all laboratory work, which involved considerable time and expense. This laboratory manual should fill this deplorable want for such books. Although the author has intended this as the "practical companion" of Professor A. P. Mathews' textbook, it can be used with ease with any text desired.

The manual is arranged in three parts: the chemistry of cell constituents, the chemistry of the digestive tract and blood and urine. These are in turn divided into

chapters dealing with individual subjects. The experiments are preceded by brief discussions of the chemistry involved, including references to the original articles. Dr Koch has not been sparing in the number of experiments presented, so that it is possible to make a choice of those that seem more pertinent for the particular course offered.

The manual is modern in every sense of the word, for the author has rejected in some parts old and customary experiments for those that have but lately been presented in the journals. This is rather markedly illustrated by the introduction of methods for quantitative glucose determinations in the urine other than the standard Benedict's quantitative test. For the most part, however, the old methods, with improvements if possible, are included along with the newer ones.

The appendix is complete with instructions to the student as to laboratory procedures and technic, with discussions as to normal and molar solutions and with methods for preparing all solutions.

Finally, it is a splendid book of its kind, up to date in its material and complete in its discussions and directions.

E M R

Recent Advances in Pathology By GEOFFREY HADFIELD, M D, F R C P (Lond), and LAWRENCE P. GARROD, M A, M D, B Ch (Camb), M R C P (Lond)
xii + 457 pages, 15 × 21 cm P. Blakiston's Son and Co, Philadelphia 1934
Price, \$4.00

The second edition of this excellent little book has been issued within two years of the first. It contains a number of additions, notably an elaboration of the authors' reasons for looking upon the major forms of anemia as primarily due to disorders of gastrointestinal function.

It is evident that judgment as to the relative importance of advances in a field as broad as that of pathology is bound to be an individual matter. The authors have made a very catholic selection of topics for discussion, grouping them partly under the systems of the body, and partly under such general headings as the reticulo-endothelial system, the deficiency diseases, the ductless glands, etc.

The discussion of the recent advances in our knowledge of cancer constitutes a valuable summary of this subject divided into chapters on carcinogenesis by irritants, the transplantation of tumors, tumor metabolism, heredity, and therapeutic cancer research. The authors have a gift of clarity of style and of concise statement, which enables them to present the complex and confusing data in this field in a clear and highly interesting way. The critical analysis of the experimental evidence adds a great deal to the value of this section. The treatment of other topics is much briefer than that devoted to the cancer problem, and though most of the sections are adequate and stimulating certain of them suffer from too great condensation. This seems true, for example, of the discussion of anoxemia which will probably seem clear only to those who are already reasonably acquainted with the subject. The statement made on page 241 that "the respiratory center responds not to a reduction of oxygen in the circulating blood but only to an increase of CO₂," is misleading. The discussion of recent work on pneumonia is even more inadequate. The types of pneumococcus are considered, but the discovery of the specific capsular polysaccharides and Avery's work on the enzyme destruction of the Type III polysaccharide are not mentioned.

The task as a whole, however, is well performed, a very clear and critical summary of many of the chief advances in the field of pathology is presented in brief form. It is a book worthy of repeated editions. The illustrations are excellent, the references well chosen. Internists will find it readable, instructive and stimulating.

M C P

The Dangerous Age in Men A Treatise on the Prostate Gland By CHESTER TILTON STONE, M D 105 pages, 14 X 20 cm The MacMillan Company, New York City 1934 Price, \$1 75

In the reviewer's opinion this book should not have been published by a reputable firm. It is the type of pseudo-scientific description of the relation of the sexual glands to sex life and to health in general that is particularly apt unnecessarily to alarm the layman for whom it is intended. According to the author, the disorders and diseases of the prostate are, with few exceptions, the commonest affecting adult males, but "by properly caring for this organ, the entire body becomes like a car brought up to date." He feels that it is safe to say that 60 per cent of all men past 40 have trouble with the prostate gland and "deferring old age resolves itself either into keeping these glands fit or into bringing them back to their proper function." "Since without sexual power there can be no real bodily and mental strength or capacity this power must be kept in a state of efficiency by the regular and proper exercise of the sexual functions." On page 51 a case is cited to support this need of intercourse. A widower develops prostatic symptoms and is advised to remarry. Failing compliance in this or in medical treatment it is stated that "the prostate would have gone on swelling until finally a tumor of the prostate developed."

The several chapters on the horrors of prostatitis, seminal vesiculitis, etc., are not only full of exaggerated and incorrect statements, but are calculated to give to laymen an entirely false idea about the efficacy of local treatment of the prostate. The book as a whole constitutes an abuse of the physician's privilege of advising the public.

M C P

Medicine, a Voyage of Discovery By JOSEF LOBEL, translated from the German by L. MARIE SIEVEKING and IAN D. MORROW 334 pages, 15.5 X 22 cm Farrar and Rinehart, Murray Hill, New York 1934 Price, \$3 00

Here are 16 essays telling the story of medicine in a somewhat different way from that ordinarily used. The first and last articles are on medicine and the others take up biology, anatomy and the other branches of the healing science and art. It is a book written by a man of wide learning and true culture who appreciates how medicine came into being and what it really is all about. The book is well translated and conveys the charm which must characterize the original. There is a slip by the translators who use the word typhus where they should have employed typhoid but it is a natural one considering the term as it is used in German.

The author does not give the earlier physicians their due. He fails to mention Minot in connection with the account of pernicious anemia, contenting himself with setting it down as an American contribution. There are a few other omissions of the same nature. He spells the anatomist Monro's name with an *e* added and leaves one a little confused as to where the resurrectionist scandal took place. These are in themselves small matters, for the book is a fine one, suited for medical men and particularly for medical students and nurses, to say nothing of the well educated layman. It will make a most acceptable Christmas present.

J R

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the following donations by members to the Library of the College by the authors

Dr R Manning Clarke (Fellow), Los Angeles, Calif —1 book, "Diseases of the Heart"

Major J R Darnall (Fellow), Ancon, C Z —2 reprints

Dr Ralph W Mendelson (Fellow), Albuquerque, N M —1 reprint

Dr Oscar W Bethea (Fellow), professor of therapeutics, Graduate School of Medicine, Tulane University, New Orleans, La, delivered the commencement address at the one hundred and twelfth annual commencement of the Philadelphia College of Pharmacy and Science during June. He was the recipient of the honorary degree of Master of Pharmacy from the College, as was also Dr Walter Bastedo (Fellow) of New York City

Dr Edgar Erskine Hume (Fellow), Major (M C), U S Army, was the recipient of the honorary degree of Doctor of Laws at the last annual commencement of Georgetown University

Dr David P Barr (Fellow), St Louis, Mo, has been giving a course of lectures on diseases of the endocrine glands at the University of Melbourne, Australia, during the past summer

Dr Frederick H Lamb (Associate), Davenport, Iowa, is the newly installed president of the American Society of Clinical Pathologists

Dr Kennon Henry Dunham (Fellow), Cincinnati, Ohio, is the newly elected president of the National Tuberculosis Association

Dr James P Leake (Fellow), senior surgeon, U S Public Health Service, has been relieved from duty in the division of sanitary reports and statistics and assigned to duty in the division of scientific research, effective June 23. He is in California cooperating with health officials in combatting the recent outbreak of poliomyelitis

Dr Frederick K Herpel (Fellow), West Palm Beach, Fla, is the newly elected president of the Florida Radiological Association

Dr Howard T Karsner (Fellow), Director of the Institute of Pathology of Western Reserve University, Cleveland, Ohio, will attend the triennial conference in Europe of the International Society for Geographic Pathology, meeting in Utrecht, Holland, of which he is a member of the Directorial Committee of five members. Later he will visit laboratories in London and Cambridge, England, Hamburg and Freiburg, Germany, and Strasbourg, France

Dr William H Walsh (Fellow), hospital consultant, of Chicago, sailed July 21 for Leningrad, where he will make an independent study of health and hospital conditions and practices in the U S S R. Dr Walsh's itinerary will take him to Leningrad, Moscow, Kharkov, Odessa, Kiev and Minsk, returning in September via Warsaw, Berlin and Paris

Dr B S Pollak (Fellow), Medical Director of the Hudson County Tuberculosis Hospital and Sanatorium, Secaucus, N J, has announced the initial work on the construction of a new 25-story tuberculosis hospital

Dr Grafton Tyler Brown (Fellow), Washington, D C, was recently elected president of the Georgetown Clinical Society

Dr Alexander B Moore (Fellow), Professor of Roentgenology at the Georgetown University School of Medicine, Washington, D C, delivered the Russell D Carman Memorial Lecture on "Function of the Roentgenologist in the Diagnosis of Intra-Abdominal Conditions" at the eighty-first annual session of the Minnesota State Medical Association held in Duluth, July 15 to 18

Dr Willard Cole Rappleye (Fellow), Dean of Columbia University College of Physicians and Surgeons, has been appointed Dean also of the School of Dental and Oral Surgery, beginning July 1

Dr Bailey K Ashford (Fellow), retired Colonel of the Medical Corps of the U S Army, has just published an autobiography, "A Soldier in Science" A dinner in honor of Dr Ashford was held at the Harvard Club, June 27, sponsored by New York physicians and officials of the Pan American Medical Association, in recognition of his contributions to tropical medicine

Dr Hillyer Rudisill, Jr (Fellow) has been made Professor of Roentgenology in the Medical College of South Carolina

The National Research Council has announced the following grants in the field of medical sciences to Fellows of the American College of Physicians

Dr John A E Eyster, Professor of Physiology, University of Wisconsin Medical School, the electrical field around the contracting heart and skeletal muscle and related phenomena

Dr Frank A McJunkin, Professor and Head of the Department of Pathology, Bacteriology and Preventive Medicine, Loyola University School of Medicine, Chicago, extraction and purification of agents that inhibit mitotic proliferation in the kidney

Dr Edward B Krumbhaar (Fellow), Philadelphia, was elected President of the American Association of the History of Medicine at its last annual meeting in Cleveland, June 11

Dr William S Middleton (Fellow), Madison, Wis, was elected a Vice-President, and Dr E J G Beardsley (Fellow), Philadelphia, Secretary

Dr Alfred Friedlander (Fellow), Professor of Medicine, University of Cincinnati College of Medicine, has been appointed Dean of the College to succeed Dr Arthur C Bachmeyer, resigned Dr Friedlander will assume office September 15

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THE MONOCYTE, MONOCYTOSIS, AND MONOCYTIC LEUKOSIS. A CLINICAL AND PATHOLOGICAL STUDY *

By CHARLES A. DOAN, M D, F A C P, and B. K. WISEMAN, M D,
Columbus, Ohio

THE MONOCYTE AND THE CELLS OF THE BLOOD

THE MONOCYTE AND THE CELLS OF THE CONNECTIVE TISSUES

THE MONOCYTE IN PATHOLOGIC STATES

THE MONOCYTE IN LEUKEMIA

CHRONIC MONOCYTIC LEUKEMIA

MONOCYTIC LEUKEMIA WITH ALLUKEMIC PHASE, LEUKEMIA CUTIS

ACUTE MONOCYTIC LEUKEMIA

THE PROBLEM OF MIXED LEUKEMIA

ETIOLOGIC CONSIDERATIONS

DISCUSSION

SUMMARY

MODERN cytologic, physiologic and pathologic studies have left little doubt as to the separate identity and functional independence of the monocyte of the blood and connective tissues. Adequate criteria in fixed as well as supravital technics are now available for sharply differentiating this strain of cells from the other leukocytic elements in the circulating blood, and important new diagnostic and prognostic interpretations of great significance are attaching to the data rapidly accumulating from the newer blood studies in such conditions as tuberculosis,¹⁻⁶ pneumonia,⁷ Hodgkin's disease⁸ and syphilis,⁹ to mention only the more outstanding examples.

THE MONOCYTE AND THE CELLS OF THE BLOOD

The history of the changing conceptions, which have from time to time been held concerning the monocyte, follows closely the development of new technics, each bringing its additional clarifying criteria of physiologic or morphologic significance to the problem. The monocyte was first considered in the original Ehrlich classification as a transitional form in the maturation of the neutrophilic leukocyte. Naegeli concurred in this view. With the introduction of the Romanowsky methylene blue-azur staining

* Read in part before the American College of Physicians, Chicago, Ill., April 17, 1934.
From the Department of Medical and Surgical Research, Ohio State University.

technic, Michaelis and Wolfe¹⁰ (1902) observed that monocyte and lymphocyte both contained azur granules, the neutrophils having quite different specific granular bodies, and Pappenheim and Ferrata¹¹ conclusively demonstrated in 1911 the independence of blood monocyte and granulocyte. The fact that monocytes are found only under pathologic conditions in the bone marrow¹² but may be found regularly arising in the spleen¹³ and peripheral lymph nodes,¹⁴ further tended to link monocyte and lymphocyte, and the evidence of tissue culture¹⁵ has been interpreted in support of a genetic relationship between these two cell strains. The azur granules, however, of the lymphocyte are relatively large, few in number, and inconstant in a clear cytoplasm, while the azurophilic granules of the human monocyte are tiny, usually extremely numerous, and imbedded in a dense, opaque, moderately deeply basophilic background. Schilling-Torgau,¹⁶ carefully analyzing these differential morphologic criteria, in 1912 definitely described the monocyte as making a third strain of the white cells, distinct on the one hand from lymphocytes and on the other from granulocytes, and thereby became the first hematologist prepared to recognize any dyscrasia specifically involving the monocyte. It is not surprising, therefore, that the very next year, 1913, Schilling-Torgau with Reschad¹⁷ should have discovered and reported the first case of monocytic leukemia. The more recent studies of the monocyte by Sabin and her coworkers² and of the lymphocyte by Wiseman¹⁸ have produced a new wealth of evidence substantiating the independence of each of these cell strains and their frequent reciprocal relationship to each other in various pathologic states.

THE MONOCYTE AND THE CELLS OF THE CONNECTIVE TISSUES

There still exists, however, a widespread skepticism as to the existence of a leukemic state involving primarily and solely this so-called monocyte of the blood and its anlagen in the connective tissues. This is explainable perhaps upon two grounds: first, a continuing inability on the part of the average physician and laboratory technician to identify and sharply differentiate in ordinary blood films this distinctive cell type, and second, a confusion relative to nomenclature, functional specificity, and morphologic differentiation of the cells of the connective tissues which is quite as profound and widespread as that involving the cells of the blood. Ranvier¹⁹ in 1891 described the powers of phagocytosis exhibited by certain free connective tissue cells which he termed "clasmatocytes." Metchnikoff²⁰ (1883-1892) then differentiated the circulating ameboid phagocytic polymorphonuclear cells of the blood, "microphages," from the relatively less ameboid phagocytic "macrophages" of the tissues, including among the latter the stellate cells of Kupffer in the liver, certain endothelial cells and the large mononuclear cells of the tissues, splenic pulp and lymph nodes. Marchand²¹ demonstrated the derivation of clasmatocytes from mesenchymal elements more especially those found in the adventitial sheath of

blood vessels, and showed that in inflammation these adventitial cells were transformed into the macrophages of Metchnikoff Maximaw²² (1902) also studied the mononuclear ameboid phagocytes in inflammatory tissues calling them "polyblasts" Ribbert²³ (1904) then found that cells of this group picked up colloidal suspensions of various composition, as for example sugar of iron, and that they segregated non-toxic dyes such as lithium carmine when the latter were introduced into the blood stream This intravital reaction was quite specific in that general vascular endothelium and fibroblasts took a negligible part in the phagocytic phenomenon, and muscle fibers rejected these vital dyes entirely Goldmann²⁴ and his associates followed with a study of the cells reacting to pyrrhol blue, demonstrating the identity of Ranvier's clasmotocytes with Marchand's adventitial cells and Maximaw's polyblasts In 1913 Aschoff and Kiyono²⁵ introduced the term "histiocyte" to designate this mesenchymal mononuclear phagocyte of the connective tissues and popularized the reticulo-endothelial concept based upon the observed degree of intensity and frequency of phagocytosis by this specific group of cells in the connective tissues

This was the general situation when interest became aroused in a new range of criteria for differentiating the mononuclear cells of the blood afforded by the application of neutral red and Janus green to living cells through a supravital technic While practically the whole experience with tissue culture^{26, 27} up to the present time has tended to strengthen the position that monocyte of blood and clasmotocyte of tissue are but different phases in the life cycle of one strain of cells,—the connective tissue macrophage,—both supravital-morphologic and clinical-pathologic studies have been accumulating which provide pertinent data raising at least a reasonable doubt as to the validity of this conclusion When the living cells are studied supravitaly, the monocyte, whether in the blood or in the tissues, reacts to the neutral red with a rosette of small vacuoles staining a characteristic uniform salmon pink and arranged more or less symmetrically in a concentric halo about the centrosphere in the hof of the nucleus Dark field examination of fresh unstained blood films confirms this pattern as indigenous to the normal living cells and not an artefact or the result of a toxic reaction to the dyes Neither lymphocyte, granulocyte nor clasmotocyte contains such a pattern of vacuoles, either in the presence or absence of the dyes mentioned, and the pH of the intravacuolar fluid in the monocyte as revealed by the indicator neutral red (pH 6.8–8.0) is so constant as to give a uniform tinctorial reaction which characterizes the monocyte throughout the animal kingdom These structures so readily demonstrated in the living monocyte are not identical with the azurophilic granules revealed in the fixed films stained with the Romanowsky dyes Furthermore, a careful quantitative survey of peroxidase stained films usually rewards the discriminating searcher with definite differences in the degree and distribution of oxidase granules in the monocytes as contrasted with granulocytes,²⁸ the

lymphocytes always, of course, being oxidase negative. The first specific vacuoles appear, as do the granules of the myelocyte, in a primitive basophilic cell, the *monoblast*, which passes through a developmental period consisting in the gradual elaboration of these structures before functional maturity and motility appear.²⁰ Unlike the definitive granulocytes and erythrocytes, the monocyte of the circulation continues to show numerous mitochondria and retains the power of mitosis, division figures being encountered not infrequently in the blood stream under relatively normal conditions. The clasmatoocyte, in contradistinction, is seldom seen in the peripheral circulation in health.³⁰ It is usually a larger cell without apparent maturation cycle, with no cytoplasmic pattern, more highly phagocytic than the monocyte for larger bodies, such as whole red and white cells, and with segregation vacuoles reacting to neutral red in a range from yellow to deep maroon, i.e., over the entire pH indicator range of neutral red. In brief, the supravital studies of Sabin, Doan and Cunningham^{2, 31} have resulted in data which help to clarify the issues thus far discussed in three directions: (1) the rosette of vacuoles reacting to neutral red in the living monocyte, when taken in combination with other distinctive morphologic criteria, sharply differentiates this cell from each of the other types of blood and tissue cells, thus supporting and confirming the previous evidence upon which its separate identity has rested, (2) the monocyte of the blood is identical with the monocyte of the tissues and reflects directly and quantitatively the proliferative activity of these elements in the body as a whole, (3) the mononuclear phagocytes of the tissues making up the so-called reticulo-endothelial system, are of two morphologic, functional and probably genetically distinct strains, the one (the monocyte) a derivative of mesenchymal reticular tissue, the other (the clasmatoocyte) an endothelial derivative, of Kupffer cell and splenic macrophage type. While no unanimity of opinion as to its exact life history has as yet been reached, as was emphasized recently by Forkner,³² who listed no less than 19 separate views as to the origin of the monocyte, it is our belief that the clinico-pathologic evidence beginning to accumulate upon the basis of the now adequate morphologic criteria essential to the recognition and differentiation of this cell, already bids fair to confirm more conclusively a mesenchymal connective tissue anlagen for the monocyte identical with or closely similar to that from which the lymphoblast and myeloblast arise. The balance of specific differentiating stimuli at any given time or location must determine the character of the definitive cell type to be produced.

Thus, the monocyte, threatened repeatedly with incorporation into the life cycle of one or other of the firmly established strains of the white cells, and surviving this fate only to have its birthright threatened once again in the discussion as to the oneness of all mononuclear phagocytes in the tissues, has survived successfully nevertheless, these histological and physiological controversies of recent years.

THE MONOCYTE IN PATHOLOGIC STATES

Perhaps the most extensive and complete studies of the monocyte in disease have been those initiated by Sabin and her associates^{1,2} in the analysis of the cellular reactions in tuberculosis. The epithelioid cell of the tubercle has been proved to be but an altered phase in the life cycle of the monocyte. Except in caseous foci the tubercle bacilli are found almost exclusively within the epithelioid cells, apparently in symbiotic interrelationship,—a manifestation of the phagocytic receptiveness of this mononuclear cell. In experimental tuberculous disease, prior to the appearance of any increase in mature monocytes in the blood or of epithelioid cells in the tissues, a marked hyperplasia of primitive blast cells occurs at the point of lodgment of acid fast organisms.²⁹ These have been proved to be monoblasts by the subsequent observance of their speedy maturation into typical monocytes and epithelioid cells within which the tubercle bacilli are thereafter usually found. Coincident with, and not prior to, the increase of these cells in organs and tissues there appears an increase in their representation in the circulating blood. Consequently, an absolute monocytosis in the blood in tuberculosis indicates the progressive formation of new tubercles in the tissues. When taken in conjunction with the qualitative as well as the quantitative data now determinable for granulocytes^{33,34} and lymphocytes^{18,35} a valuable source of information about any given tuberculous patient is at once available.

The biological studies, however, of the chemical fractions from the acid fast bacteria have laid the foundation for the most promising conception of the nature of the fundamental stimuli responsible for monocytic proliferation. A thorough survey extending through the past decade with adequately prepared and controlled chemical fractions³⁶ has established conclusively the fact that the lipoids, more particularly the tuberculo-phosphatides, are solely responsible for the monocyte-epithelioid proliferation and differentiation in tuberculosis, and that the ultimate active principle is to be found in one or more of the newly isolated fatty acids from this material.²

It is of interest in this connection to note that a similar response to lipoids has not been observed for the clasmatocytic elements of the connective tissues. In experimental kala azar,³⁷ however, there appears to be as specific host-parasite relationship between clasmatocyte and the *Leishmania donovani* bodies as in tuberculosis between monocyte and tubercle bacilli. A sharper pathologic differentiation of these two cell types is thus exemplified in the tissue reactions of these two diseases than exists physiologically, which suggests different inherent cell-strain capacities for phagocytic response.

Other conspicuous examples of the monocytic reaction to bacterial invasion are provided in syphilis,⁹ typhoid fever,³⁸ undulant fever,³⁹ and in *B. monocyto genes* infection of rabbits.⁴⁰ In lobar pneumonia, Hickling⁷

has demonstrated a transitory reflection in the blood of an increased mobilization of monocytes in the lung during the period of resolution, the monocytosis being indefinitely maintained if empyemic complications arise. Under these circumstances the demand for an increased phagocytic function is apparent and prognostic data are accordingly enhanced when the monocyte factor is recognized.

THE MONOCYTE IN LEUKEMIA

During the latter part of the last century it was currently believed that all acute leukemias were of lymphoid origin. Fraenkel⁴¹ in 1895, among others, emphasized the lack of differentiating criteria, which marked the cells of the majority of such syndromes as lymphocytic elements. With the recognition and separation of the myeloblast on morphologic grounds by Naegeli⁴² in 1900, it became gradually apparent that many of the cases which upon superficial examination revealed a predominance of cells without the usual complement of specific granules in the cytoplasm, nevertheless represented disturbances in myelopoiesis so profound as to permit the delivery into the active circulation of greater or lesser numbers of these agranular, myeloblastic elements, usually restricted to the marrow.^{43 44, 45} The elaboration of new technics for the accentuation of the differences, which become less and less distinctive and characteristic of the respective cell strains the earlier the individual units are seen in their respective maturation cycles, has made for continued progress in the differential diagnosis of this group of leukemic dyscrasias. Schilling's comparable contribution (1912) toward the separate identity of the monocyte, laid the foundation for the recognition of the third type of leukemia, but despite Schilling's pioneer observations made more than two decades ago, a leukemia in which the monocyte seems to be primarily involved is only just beginning to be recognized sufficiently widely and frequently to furnish the basis for clinicopathologic studies leading toward the revelation of further details about this strain of cells. As may be seen from the accompanying diagram, the monocyte satisfies all of the theoretic demands necessary for the development and appearance of pathologic states parallel to and characterized by the same varying symptomatology as those involving the longer established cell strains. If the medical literature on this subject may be subjected to interpretation at all, it reveals the protean manifestation of clinical signs and symptoms which has obtained in the cases reported as suffering from monocytic leukemia. A personal experience during the past four years with some 75 cases of leukemia (table 1) of all types and degrees of severity

TABLE I

| | |
|--|--------|
| The Leukemias of All Types Studied during a Four Year Period | |
| Total Cases 1930-34 | 76 |
| Myeloid Leukemia | 28-37% |
| Lymphatic Leukemia | 36-47% |
| Monocytic Leukemia | 12-16% |

and manifesting widely divergent cellular reactions has made the present authors keenly aware that the only basis upon which ultimate differentiation of the several types can be accurately and consistently made is that which rests upon the morphologic and behavior characteristics of the circulating cells themselves as they appear under the conditions provided by supravital as well as fixed staining technics. There is no clinical syndrome in our experience which is pathognomonic of monocytic leukemia as distinct from myeloid or lymphatic leukemia. Certain generalizations have been attempted by some authors but these have been made largely from analyses of the literature since no single investigator has as yet had a personal experience great enough to draw upon statistically, and it is our opinion that up to the present moment the difficulties inherent in the differentiation and identification of lymphoblast, myeloblast and monoblast, to say nothing of more mature monocytes and myelocytes "B," have been sufficiently great to render it worse than useless to attempt to judge from "the published records" the principle underlying cellular pathology in any given case. And this is not to doubt the authenticity and existence of many more cases of monocytic leukemia than have begun to be reported. Dameshek,⁴⁶ reviewing the literature up to and including 1929, was inclined to accept 18 of the 31 then reported cases. Clough⁴⁷ in a further analysis (1932) endorsed as true instances of monocytic leukemia 22 of the then accrued 39 cases. Up to and including the early part of this year, 1934, we have found some 75 reported cases exclusive of those designated as aleukemic reticulo-endotheliosis, many of the latter doubtless belonging in this general group. Because of the reasons cited, we prefer not to attempt a critical evaluation of the individual cases. Ultimately the registry for thoroughly studied and authenticated cases of monocytic leukemia which the Clinical Pathologists have organized under Dr. Kracke's direction, will furnish the proper basis for such an appraisal and statistical analysis.

Our own experience confirms the general impression conveyed by the literature that every feature common to myeloid and lymphatic leukemia has been found in the monocytic form. Thus, monocytic leukemia has been reported as occurring at any age from 11 months⁴⁸ to 71 years⁴⁹, and it may be relatively chronic,⁵⁰⁻⁵¹⁻⁵² subacute⁵³⁻⁵⁶ or fulminant^{32, 50, 57-59, 64, 65} or it may, with leukemic or aleukemic blood, present a confusing picture of the so-called mixed leukemia type, it may be associated with a neoplastic growth⁴⁶ similar in all respects to leukosarcoma⁶², it has shown the skin manifestations of leukemia cutis⁶⁰⁻⁶³. Cases without demonstrable splenomegaly,⁴⁷⁻⁴⁹⁻⁵⁷⁻⁵⁹ lymphadenopathy⁴⁷⁻⁵⁰⁻⁶⁴ or without hemorrhagic manifestations are described⁵²⁻⁵⁷⁻⁶⁶. One or other of these variations has been reported from single case studies by individual investigators usually, but it has been possible for us to observe all of these respective clinical manifestations in the present series of nine personally studied and verified cases of the disease, and to make the diagnosis in three other patients from whom blood films have been available for confirmation of the cell type involved.

During the same period we have seen from the same general cross section of patients 28 myeloid and 36 lymphatic leukemias. Our experience would thus suggest an incidence of monocytic leukemia of 16 per cent or less, with approximately 37 per cent myeloid and 47 per cent lymphoid leukemias on the basis of 76 cases studied over a four year period. The age incidence in our series has been from four to 70 years, seven were male, five female patients, the known duration of the disease was from six weeks to four years.

CHRONIC MONOCYTIC LEUKEMIA

The verification of the existence of a relatively benign, chronic state of monocytic leukosis is essential to the full establishment of this leukocytic element on a pathologic par with granulocyte and lymphocyte. A true chronicity, however, has seldom been encountered or recognized in the leukemias of monocytic type, as judged by a survey of the literature to date, though a chronic or subacute syndrome is perhaps more commonly seen than the very acute process in the leukemias of myeloid and lymphatic origin. It happens that the first case recognized by us as coming under the general category of monocytic leukemia was encountered within the first two months of the establishment of our blood clinic at Ohio State University in the fall of 1930, and represented an extremely chronic, non-progressive syndrome, the patient eventually succumbing to cerebral hemorrhage after a year's observations without an acute exacerbation of the leukemic process at any time.

CASE I

J. G., white, male, aged 66 years, a retired hardware salesman, was first seen September 12, 1930, at the request of Dr. L. H. vanBuskirk. Following the extraction of 12 upper teeth January 28, 1930, there had been profuse hemorrhage persisting for 24 hours to the point of serious exsanguination, the patient fainting upon the least exertion. For several months thereafter he remained excessively weak and finally returned to his physician early in September saying he had been unable to regain his accustomed vigor since the experience of the preceding January. About 15 pounds in weight had been lost. A moderate hypertension (162/100) existed. The remaining teeth showed extensive caries. Heart and lungs were reported as essentially negative. The urine showed a trace of albumin and a few casts, no pus. The blood examination showed erythrocytes 3,690,000, hemoglobin 60 per cent, leukocytes 12,480, and the differential count revealed PMN 33 per cent, PME 3 per cent, myelocytes 7 per cent, lymphocytes 21 per cent, monocytes 36 per cent. An elimination of obvious toxic foci in the mouth was advised and the remaining teeth were promptly extracted. No immediate difficulty ensued but one week following the extractions a severe hemorrhage occurred from the tooth sockets persisting for 24 hours and requiring the services of a physician to control. It was at this point that consultation was requested and we had the opportunity of following personally the subsequent course of events. Our first complete studies October 16, 1930, revealed 4,250,000 red cells with hemoglobin of only 67 gm. in 100 c.c. blood, 60,000 platelets and 26,900 leukocytes with the following supravital differential: active PMN 16.5 per cent, round 2 per cent, vacuolated 0.5 per cent, non-motile 1 per cent, baso-

philes 0.5 per cent, eosinophiles 1 per cent, myelocytes "C" 1.5 per cent, small lymphocytes 10 per cent, intermediate 1 per cent, large lymphocytes 0, monocytes, active 65 per cent, clasmatoocytes 0.5 per cent, unclassified 0.5 per cent, hematocrit 31.5, average diameter erythrocytes 7.64 microns, sedimentation 25 mm in 1 hour, icterus index 9, erythrocyte fragility 0.520-0.340

On October 20, 1930 the patient was admitted to the Research Service, University Hospital, for a five day period of observation. Except for the dental condition and a moderate hypertension the patient had been in good general health prior to January 1930. In early childhood he was subject to chills and fever, presumably malaria for they were controlled with quinine. At 11 years and again at 20 he had pneumonia with, in each instance, a prolonged convalescence of 10 to 12 weeks. During seven years, between the ages of 54 and 61, recurrent attacks of jaundice associated with pain in the region of the gall-bladder were experienced. Other than on the two occasions previously mentioned no history of hemorrhages, epistaxis, or purpura was obtainable. The family history was entirely negative in so far as it might relate to the patient's present illness.

Physical examination on first admission to Hospital T 98° F, P 70, R 18. Blood-pressure, 170 systolic and 100 diastolic. Weight 138 pounds. There was a marked pallor. Nodes in the anterior cervical chain of the right side, 1 cm in diameter, were palpable with none demonstrable on the left. The posterior cervical, submaxillary, submental and epitrochlear nodes were not palpable. In the left axilla two to three small nodes 1 cm in diameter were felt but none were found on the right. A few small inguinal nodes were present. The palpable nodes were discrete, movable, elastic, not tender. The chest was negative except for a moderate degree of cardiac enlargement. The liver could be felt 4 cm below the right costal margin, the spleen was not palpable. Reflexes not remarkable.

Laboratory Studies The cytological studies of the blood may be followed on chart 1. Gall-bladder visualization was successful, no evidence of calculi was found and there was rapid emptying following the fat meal. The humerus, radius, femur and tibia on the right side showed no radiologic evidence of any pathologic process, a marked density of the bones of the skull was apparent. Blood chemistry NPN 28, urea nitrogen 11.4, urea clearance 46.2. Blood culture, negative. The basal metabolic rate was plus five and plus ten on two days. Tuberculin Mantoux tests (human, bovine and avian) were all negative. Urinalyses showed granular casts (two plus), and albumin 25 mg. Phosphatid precipitin test, antigen A-3 H-37, positive 1-1280. An exploratory biopsy failed to yield the desired lymphatic tissue for histologic study.

In brief, the hospital study failed to reveal any apparent cause for the abnormal differential blood count, but confirmed beyond any reasonable doubt the monocytic character of the established mononuclear predominance in the circulation of this patient. A three hour study with observations taken at 15 minute intervals in order to appraise the rhythmic cycle of the different cellular elements showed a disordered mechanism for the monocytes, which together with the shift to the left with a dominance of quite young forms among this group, served to establish the diagnosis of chronic monocytic leukemia. The relative but not absolute decrease in granulocytes and lymphocytes with their more moderate "shift to the left" and relatively unaffected normal rhythm suggests a secondary rather than a primary participation of these elements in the syndrome.

Little change was noted during the succeeding months except that the hemoglobin increased to 12 gm per 100 cc of blood by January 1931 and the platelets increased to between 130,000 and 350,000 with no hemorrhagic tendencies manifest. Desired activities were not denied the patient, and he enjoyed a relatively normal life. The total white count ranged between 15,000 and 30,000, with the monocytes representing from 11,000 to 22,000 cells.

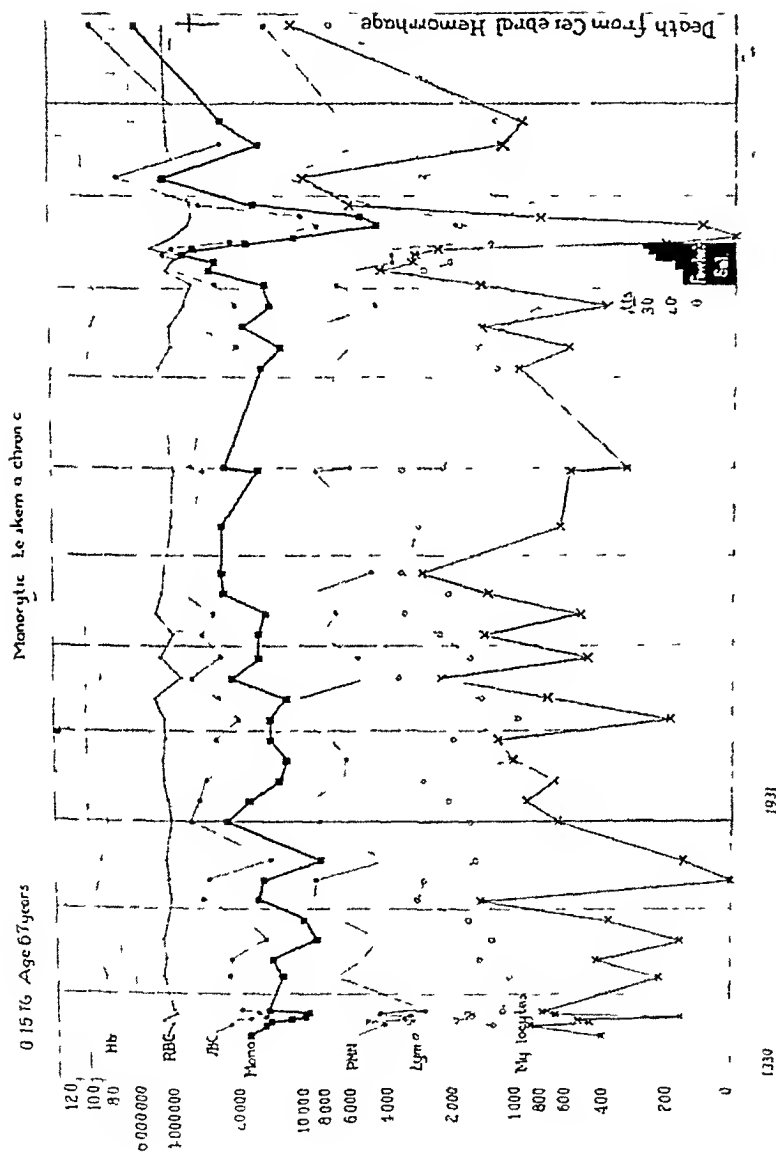


CHART 1 This patient showed a persistent monocytic elevation largely responsible for the increase in total leukocyte count, but without significant clinical symptoms of leukemia, during the year of observation. The lymphocytes were unchanged either in quality or quantity. Myelocytes were consistently present, fluctuating between 200 and 2,000 per cu mm. During the period of arsenic medication the myelocytes were reduced as well as the mature granulocytes, but on the rebound following the stopping of the medicine they rose to a high point of 9,000 per cu mm. Following the cerebral hemorrhage the terminal blood picture showed 14,000 mature granulocytes, 11,000 myelocytes, 7,000 lymphocytes and 60,000 monocytes. (See plate 3, figures 1 and 6, for the type of monocyte involved.)

With the hope of increasing the reserve of the patient's strength by attempting to establish the white count on a lower level with a more nearly normal differential, it was decided in July 1931 to institute arsenic therapy in the form of Fowler's solution. As is usual when this treatment is used in myeloid leukemia a definite increase in total count was noted during the first ten days of medication up to 42,000, the increase being specifically due to a relative and absolute increase of monocytes, from 60 per cent to 80 per cent of all cells, or from 14,000 to 34,000. Granulocytes and lymphocytes were essentially unaltered except that the granulocytes were decreased during the period of lowest total white counts (8,000) at the end of the period of medication. Starting with five drops three times a day the dose was gradually increased until the white count had been reduced to 20,650 by the end of the seventeenth day with a maximum dosage of 33 drops per day. Definite toxic symptoms appeared at this time. The medication was immediately stopped, and within the following 48 hours all acute symptoms had passed. The total white count at this time was 13,850. Three days later the white count reached its lowest level of 8,350, with 23 per cent neutrophils, 1 basophile, 1 myelocyte, 22 per cent lymphocytes and 53 per cent monocytes. A rapid rebound in the total count and its constituent elements, more particularly the monocytes and myelocytes, carried the cells to a new high of 68,000 per cu mm during the ensuing two weeks with a return to the premedication equilibrium one week later.

During August and September the patient was in unusually good health and spirits. On September 26 he was suddenly seized with generalized convulsions in his home. The patient was immediately transferred to the Hospital where the convulsive seizures were readily controlled with luminal sodium. The white count on admission was 90,000 with 68 per cent very young monocytes (Plate 3, figure 1). The patient died in coma at 7:30 the following morning.

Postmortem examination was made by Dr Ernest Scott, late Pathologist to the University Hospital, at 11:30 a.m. Nothing remarkable on external examination, no generalized adenopathy. The peritoneal lining was smooth and glistening. The liver was at the costal margin, normal in size and appearance except for some slight thickening of the capsule in places, with no gall-bladder lesion. The spleen measured 15 by 9 by 4 cm and weighed 260 grams, it was brick red in color, firm with some mottling of the cut surface and an absence of follicles. The stomach, the small and large intestines, the pancreas, both adrenals and the prostate gland were normal to gross examination. The kidneys were normal in size, the capsules were adherent and there were cortical cysts measuring as much as 1.5 cm in diameter, each kidney presented a dilated pelvis and thinned out cortex, both ureters were normal, the urinary bladder was normal. The pleural cavities were free of adhesions and showed no increased fluid. The lungs were air containing throughout, the vessels and bronchi at the hilus were normal, an old scar was found at the right apex but no evidence of tuberculosis was present. The hilus lymph nodes were

PLATE I

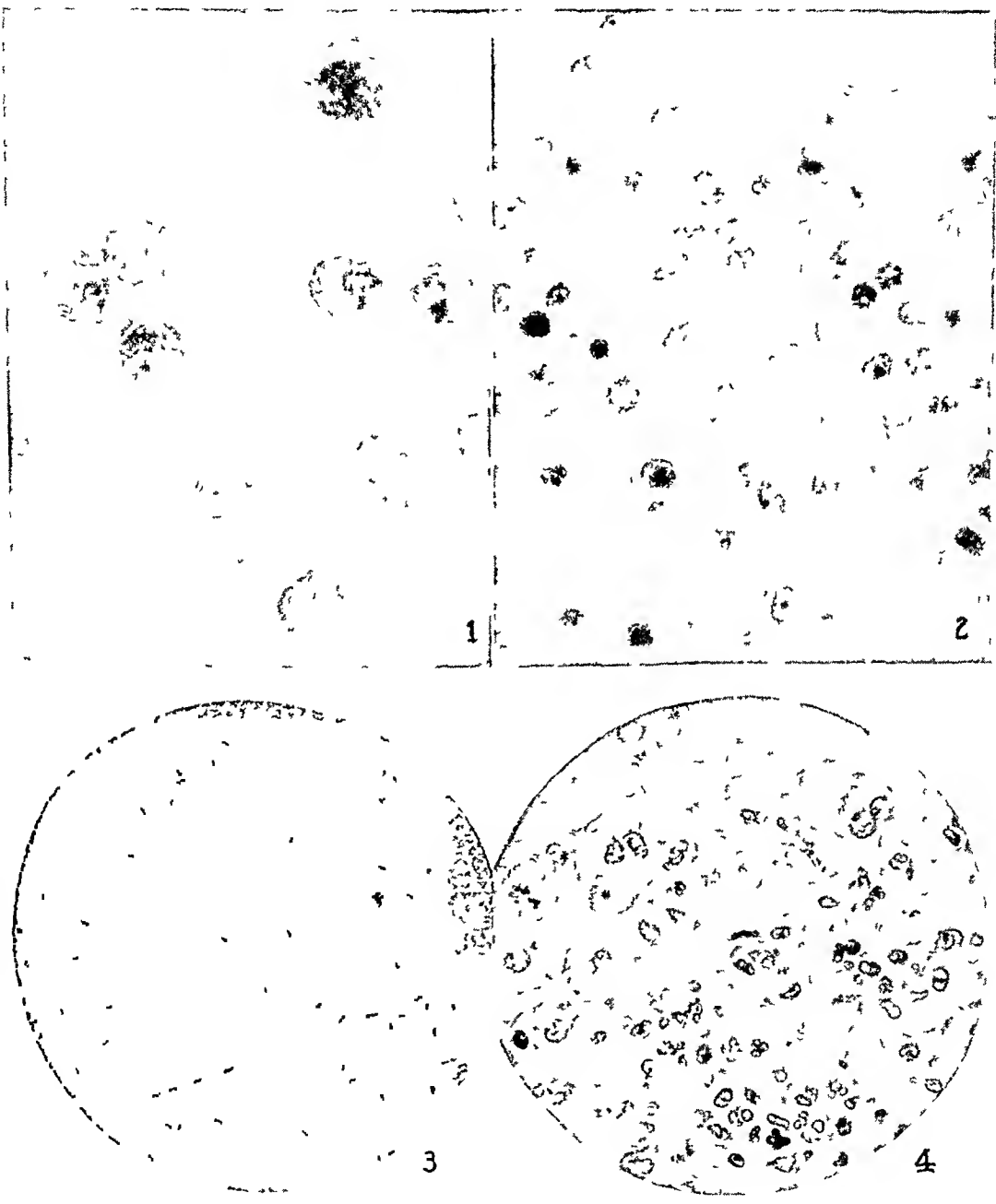
FIG 1 Photograph of blood film stained with Wright's-Giemsa taken from Case II during the terminal leukemic phase. Monoblasts and young monocytes, one showing a small vacuole, make up the entire leukocytic picture of this field. $\times 960$

FIG 2 Case I Chronic monocytic leukemia. Photomicrograph of the femoral bone marrow showing the hyperplasia of monocytic elements with typical nuclear characteristics. Oil immersion, $\times 960$ H and E.

FIG 3 Case VIII Acute monocytic leukemia. Foci of monocytic cells scattered throughout the liver, more frequently periportal in location. Low power $\times 100$.

FIG 4 Case VIII A higher power of the liver of figure 3, showing the character of the cellular proliferation. The monocytic hyperplasia is encroaching upon the liver cells which show large cytoplasmic vacuoles and evidence of nuclear degeneration. Oil immersion $\times 960$.

PLATE I



anthracotic but not enlarged. The mediastinal nodes were not remarkable. The heart weighed 500 grams, there was a moderate increase of pericardial fluid, no adhesions, the valves were intact. Bone marrow, secured from ribs, sternum, vertebra and femur, was everywhere abundant, dark red in color, and apparently hyperplastic. The scalp, calvarium and dura mater presented no noteworthy changes. Upon examining the hemispheres, however, the left frontal lobe was seen to be definitely enlarged, extending beyond the midline, compressing the inner surface of the right hemisphere, the convolutions being flattened and the sulci greatly narrowed over the surface. There was a congestion of the capillaries of the pia, the vessels at the base and the basilar and internal carotid arteries showed moderate sclerotic changes. Upon section after fixation a large blood clot filling the entire anterior horn of the left lateral ventricle and involving all of the adjacent tissue was found, being limited by a very thin margin of brain substance.

Microscopic Examination. *Supravital preparations* of the fresh tissues as well as fixed sections were studied. *Brain.* The vessels of the cerebellum and medulla were thickened and their lumen filled with masses of mononuclear cells. In the margin of the clot were to be found many monocytes singly and in large clumps. At some distance from the main hemorrhage there were areas of monocytic cells in the brain substance, many of which were surrounded by definite small hemorrhages. *Liver.* Sections showed an early cirrhosis, venous congestion and small accumulations of monocytes. *Spleen.* The Malpighian bodies were practically obliterated by the hyperplasia of large clear mononuclear cells with vesicular nuclei of varying size and contour and number, and by hemorrhage. There were many eosinophiles and some increase in fibrous tissue. The histo-pathologic picture was not unlike that seen in Hodgkin's disease. *Lymph Nodes.* As many lymph nodes as could be found, including axillary, mesenteric, retroperitoneal, mediastinal and peri-bronchial, were studied, all showing approximately the same pathologic changes: decrease or absence of normal lymph follicles, hyperplasia of large mononuclear cells with bizarre shaped vesicular nuclei, some increase of reticular and fibrous tissue and very many eosinophiles, with an occasional tissue basophile and plasma cell. (See figures 7 and 8, plate 2.) As in the case of the spleen the resemblance to Hodgkin's pathology was striking. *Bone Marrow.* All marrows showed a non-erythropoietic hyperplasia with a diminution in the usual fat content. Intimately intermingled with the myelocytic elements were small groups of monocytes, not present under normal conditions, with the characteristic nuclear abnormalities which suggest a disordered division mechanism. (See figure 2, plate 1.) Erythropoiesis and myelopoiesis were apparently progressing in an orderly sequence except that the myeloid cells showed a greater shift to the left with more of the early myelocytes and myeloblasts present than occur under strictly physiologic conditions. *Kidneys.* Sections showed advanced arteriosclerotic changes, but no monocytic foci.

PLATE II

FIG 5 Case VI. Acute monoblastic leukemia. Photomicrograph of femur bone marrow showing three mitotic figures and the monocytic replacement of myeloid and erythropoietic tissue. Note absence of usual fat cells. Oil immersion, $\times 960$.

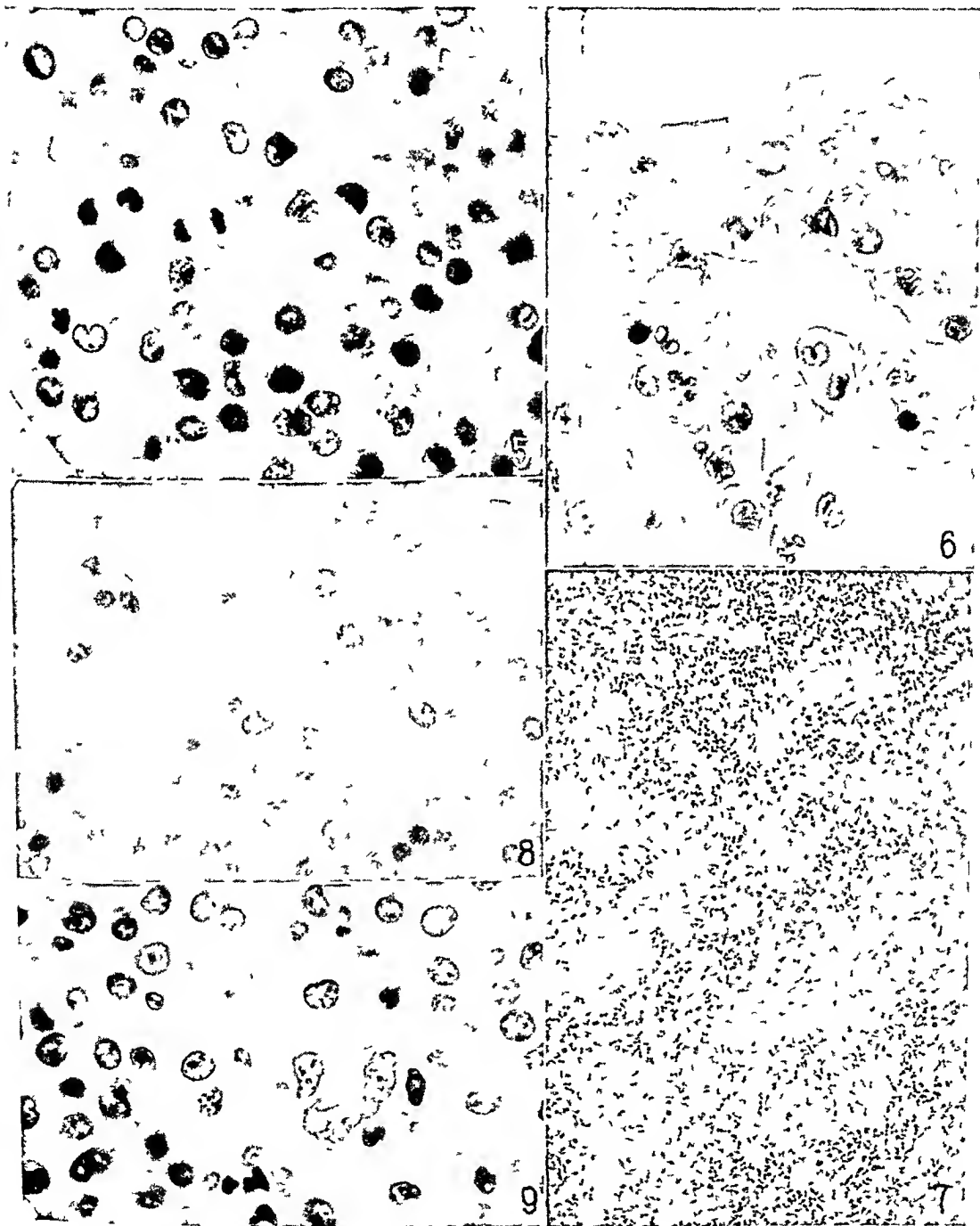
FIG 6 Case VIII. Acute monocytic leukemia. Photomicrograph of the lung showing intraseptal proliferation and accumulation of monocytic elements with characteristic nuclei. Oil immersion, $\times 960$.

FIG 7 Case I. Chronic monocytic leukemia. Axillary lymph node showing the disordered architecture of the gland with almost complete replacement by monocytes and fibroblasts of normal follicles and germinal centers. 16 mm objective, $\times 100$.

FIG 8 Case I. Higher power of the lymph node of figure 7, showing the character of the cells which have displaced the lymphatic elements. Oil immersion $\times 960$.

FIG 9 Case VI. Acute monoblastic leukemia. Bone marrow from the tibia to contrast the monoblastic cells with a megakaryocyte. Oil immersion, $\times 960$.

PLATE II



other than the intravascular accumulations of cells. *Adrenals* An adenoma of the adrenals was revealed on microscopic examination. *Lungs* The alveoli in certain areas were filled with a serous exudate with some neutrophilic leukocytes and fibrin. Other tissues were not remarkable from the standpoint of the monocytic dyscrasia.

In summary, we have a case in which all of the essential criteria for a chronic monocytic leukemia were met. The patient was followed through a 12 months' period without leukemic exacerbation and postmortem confirmation was obtained of death from cerebral hemorrhage upon a hypertensive arteriosclerotic basis. No active tuberculous focus was found. The tissue evidence, particularly in the bone marrow, spleen and lymph nodes, substantiated the existence of a relatively benign leukemic process primarily involving the monocytic strain of cells.

A very similar case has been studied by Dr Hildegard Henderson, formerly associated with us in this laboratory, now of San Francisco, California. The patient a white female aged 53 years, was first seen in July 1930 with complaints of sharp pain on the right side radiating to the back, night sweats, and easy fatigability. The menopause had occurred five years previously. Two months before admission there had been profuse vaginal bleeding which persisted for two weeks and was followed by tarry stools for two weeks. A peri-nephritic abscess, yielding *B. coli*

PLATE III

Maturation of the monocyte as illustrated from selected cases of monocytic leukemia. The maturation of the monocyte and its life cycle have been followed under normal conditions and in experimental tuberculosis, and the evidence now accumulated in the study of monocytic leukemia is supplementary to and in complete conformity with that already adduced. All cells are drawn from Wright's-Giemsa stained blood films.

FIG 1 Case I. Monoblast representative of the type of cell which appeared in increased numbers in the peripheral blood following cerebral hemorrhage in a case of chronic monocytic leukemia otherwise showing no exacerbation during a year's observation. Dense blue cytoplasm, purple mottled nuclear chromatin, fairly large spherical nucleoli. Size 14.5 microns.

FIG 2 Case II. Monoblast of slightly later stage than figure 1 with the dense basophilia partly lost. No azurophilic granules are to be seen but the nucleus is typical. This cell and that of figure 3 were characteristic of the terminal stage in a case which 5 months previously had shown an aleukemic phase. Size 15.2 microns.

FIG 3 Case II. Monoblast with large single nucleolus, but a cytoplasm less densely basophilic than in the two preceding cells. Some mottling of the cytoplasm and a suggestion of beginning vacuolation may be seen, but still no azurophilic granulations. This cell is typical of the majority of monoblastic cells seen in the peripheral blood in the acute stages of the disease. Size 17.5 microns.

FIG 4 Case VI. Young monocyte with two nuclei in an acute case. A few, fine azurophilic granules may be seen in the cytoplasm. Multinucleated monocytes are encountered frequently both in the blood and in the tissues in monocytic leukemia. Size 16.1 microns.

FIG 5 Case V. Vacuolated monocyte, a constant finding throughout the five months' duration of the disease in this case, both in the earlier aleukemic phase and in the terminal acute leukemic exacerbation. Vacuolation occurs much more frequently in the monocyte and in the leukemic monocyte than in the other types of white blood cells. Size 16.8 microns.

FIG 6 Case I. Normal adult monocyte with characteristic indented nucleus and fine azurophilic granulations, this was the predominating type of cell present throughout the period of observation of a year in this patient during all of which time there was a definite elevation of the total leukocyte count with idiopathic monocytosis. Size 16.8 microns.

was found and surgically treated without sequelae or complications. The blood studies at this time showed a total white count ranging from 6,000 to 13,000 with neutrophilic leukocytes 24-43 per cent, lymphocytes 20-40 per cent, monocytes 25-28 per cent, red blood cells 3,470,000, hemoglobin 72 per cent. Since that time the monocytes have gradually increased. In March of this year, the total count was 11,350 and the hemoglobin 85 per cent, our differential from the blood films furnished by Dr. Henderson showed neutrophilic leukocytes 5 per cent, basophiles 1 per cent, faintly basophilic lymphocytes (O) 4 per cent, moderately basophilic lymphocytes (M) 10 per cent, deeply basophilic lymphocytes (Y) 19 per cent, mature monocytes (some vacuolated and some with two nuclei) 57 per cent, young monocytes 2 per cent, non-phagocytic clasmotocytes 1 per cent. No adenopathy and no splenomegaly have been observed at any time. No tuberculous activity can be demonstrated. Aside from an increasing ease of fatigability and "nervousness" there are no complaints. The profound neutropenia is significant as is the "shift to the left" in the lymphocyte formula. A chronicity of the process continues, whatever may be the underlying pathology, and whether the gradually increasing monocytosis without a definitely elevated total count is reflecting a leukemic proliferation of these elements in the bone marrow must await perhaps further studies. No other diagnostic entity can explain the picture at the present time.

MONOCYTIC LEUKEMIA WITH ALEUKEMIC PHASE, LEUKEMIA CUTIS

Case 2 Through the courtesy of Dr. Louis I. Mitchell, of Newark, Ohio, we have been permitted to follow the course of events in a man, W. W. P., aged 63 years, a railroad engineer, whose final illness began with skin manifestations and a leukopenia and terminated some five months later in a typical leukemic exacerbation of monocytic character. Dr. Mitchell is reporting this case in detail elsewhere, so that only a brief resume will be presented here. In December 1931 the patient became conscious of a definitely increasing weakness and anemia. The following April he first noted the appearance of subcutaneous hemorrhagic areas on the inner aspect of each thigh, and at about the same time multiple small firm subcutaneous nodules developed over the lower abdomen, subsequently appearing over the body generally, including the scalp. The testes became enlarged and painful. When first seen by Dr. Mitchell early in April some 200 firm, discrete, movable, subcutaneous nodules were counted. There was no general adenopathy and the liver and spleen were not palpable. Temperature 98° F., pulse 80, respirations 20, blood pressure 120 systolic and 70 diastolic. All search for focal infection resulted in negative findings except for one molar tooth which was immediately extracted without untoward sequelae. Renal function was normal, urine was negative. The total white count was within the limits of normal, 5,000, the differential count revealed 30 per cent qualitatively normal monocytes, 28 per cent lymphocytes, 37 per cent neutrophils, 2 per cent basophiles and 3 per cent eosinophiles. While myelocytes were not observed on this first count every subsequent differential showed from 2-9 per cent myelocytes. There were 3,000,000 red blood cells and 76 gm. hemoglobin per 100 c.c. blood, the erythrocyte fragility was normal, 0.396-0.300, the sedimentation velocity 20 mm. in one hour.

Under arsenic therapy in the form of sodium cacodylate, $\frac{3}{4}$ gr. subcutaneously every 48 hours, a definite reduction in the number and size of the nodules was noted with subjective clinical improvement in the patient, although a more profound leukopenia developed with both neutrophils and monocytes obliterated from the picture for a time (chart 2). Shortly, however, more nodules began to appear even while the earlier ones were fading, and roentgen-ray and radium therapy were instituted on May 10, eleven treatments in all being given during the succeeding

three weeks. Again initial but only temporary success in reducing what a biopsy had shown to be aggregations of mononuclear cells in the deeper layers of the skin attended this therapy. By July the nodules were found to have become resistant to the measures instituted and during the latter part of this month a marked exacerbation of clinical symptoms occurred accompanied by evidences of a rapid increase in the size of liver and spleen. We were again permitted by Dr. Mitchell to study this patient in the terminal stage of his disease, in which the profound anemia and thrombopenia with hemorrhagic diathesis, and definite leukemic blood

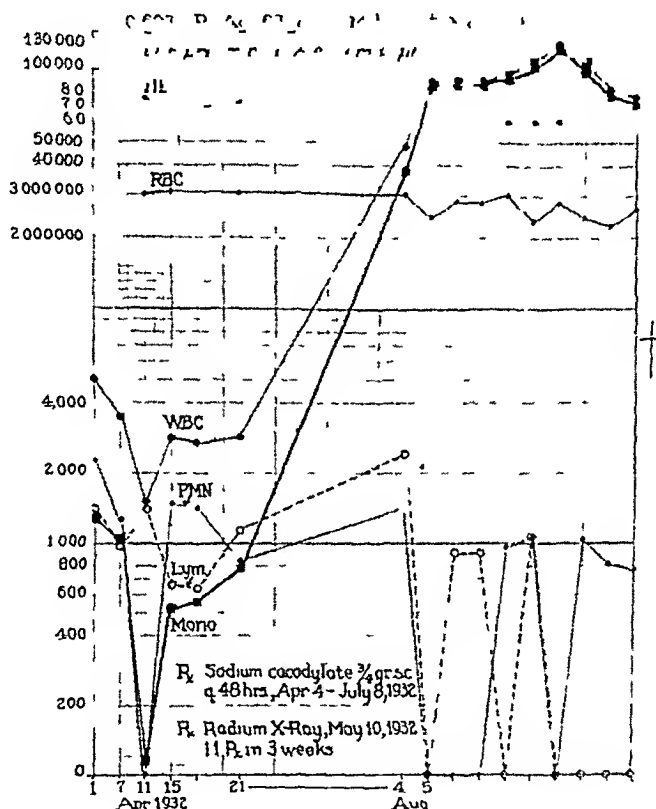


CHART 2 The aleukemic phase with marked skin involvement but minimal constitutional symptoms extended over a known period of five months in this case and probably for some four to six months prior to diagnosis. The terminal clinical and laboratory picture of acute monoblastic leukemia showed the total white count of 130,000 to be comprised almost exclusively of monoblastic elements. (See plate 3, figures 2 and 3)

left no doubt as to the diagnosis of the original clinical manifestations. A predominance of very immature mononuclear cells, monoblasts and young monocytes, marked the white cell differential in this case (Plate 1, figure 1, plate 3, figures 2 and 3). On the day prior to death serial counts taken at 15 minute intervals for two hours revealed the erratic maturation and delivery of monocytes in an absolutely disordered mechanism of cellular proliferation which characterizes the leukemic state.⁴⁴ The erythrocyte fragility had changed from the normal of five months before to the leukemic range, 0.471-0.341, the icterus index was 9, the erythrocyte hematocrit was 27, the leukocyte packed cell volume 6.

The tissues secured at a partial postmortem by Dr Mitchell and forwarded to this laboratory for section and study confirmed the clinical and laboratory diagnosis of monocytic leukemia. Liver, spleen, bone marrow and lymph nodes have proved in all cases thus far studied in this series to be of greatest significance from a pathologic standpoint. The liver and spleen in this patient were markedly enlarged. The liver revealed on microscopic examination marked hyperplasia of typical large mononuclear cells with vesicular nuclei of bizarre shape and number with usually one, never more than two, nucleoli. The normal architecture of the spleen was completely destroyed by the overgrowth of monocytic cells, comparable in all respects to the cells found in the circulating blood, in the skin nodules at biopsy and in the other organs mentioned at autopsy. The bone marrow everywhere was hyperplastic with non-hemoglobin bearing elements, the leukemic cells being quite distinct morphologically from the myelocytic cells among which they were scattered and upon which their rapidly proliferating mass was obviously encroaching.

This case exemplified three interesting manifestations of monocytic leukemia: (1) initial chronicity, (2) an initial leukopenic or aleukemic phase, (3) spontaneous, specific, widespread proliferation in the general connective tissues of an indigenous connective tissue element, the monocyte, at a time when the absence of any excess of these cells in the peripheral blood eliminated the possibility of an infiltrative mechanism to explain the formation of the subcutaneous nodules. This last evidence is akin to that obtained in the experimental studies of tuberculosis, in which tissue and organ proliferation of monoblasts, monocytes and epithelioid cells definitely precedes the appearance of increased numbers of monocytes in the peripheral circulation. This sequence of events holds both for the disease itself,¹² and for the reactions following the exhibition of tuberculo-phosphatid into the body.²

Cases 3 and 4 have been studied through the courtesy of Dr S T Mercer, of the Vanderbilt Clinic, the Medical Center, New York City, who recognized and diagnosed the blood dyscrasia and its type in these two patients from the clinical history and character of the skin lesions, the latter having presented as one of the chief complaints in the syndrome. Both were acute cases of rather short duration, with no preceding illness, and with definite leukemic blood pictures of typical, characteristic monocytic dominance. One of these patients we saw in person, and had the opportunity of studying the supravital characteristics of the cells of the blood, as well as those presented in the fixed films. The other was studied only through the fixed blood films and the sectioned material secured at biopsy when representative skin nodules were obtained. The findings already listed as cytologically significant in monocytic leukemia were all present in these cases and the detailed data important to the recognition of monocytic leukemia cutis and its differentiation from the skin lesions in leukemic states of other cytologic origin and from non-leukemic dermatoses, are being presented by Dr Mercer elsewhere.

Case 5 is again a case referred to us for an opinion as to the differential diagnosis by Dr E W Mitchell of Cincinnati, Ohio. Dr Mitchell kindly furnished us with a series of blood films covering the period of observation from June 15, to December 15, 1933, showing the gradual transition from an initial aleukemic state into the terminal leukemic syndrome of typical monocytic predominance (Chart 3). The history and clinical course are quite similar to those of Case 2, except for the absence of skin manifestations, the duration of the disease in each instance

was between five and six months. From the very beginning in this case, a careful survey of the cells in the peripheral blood revealed not only a relative increase in the number of monocytic cells but also qualitative changes which could not be mistaken. As is so much more frequently found with monocytes than with the other white blood cells, very many of these specific elements showed large, clear, vacuolar

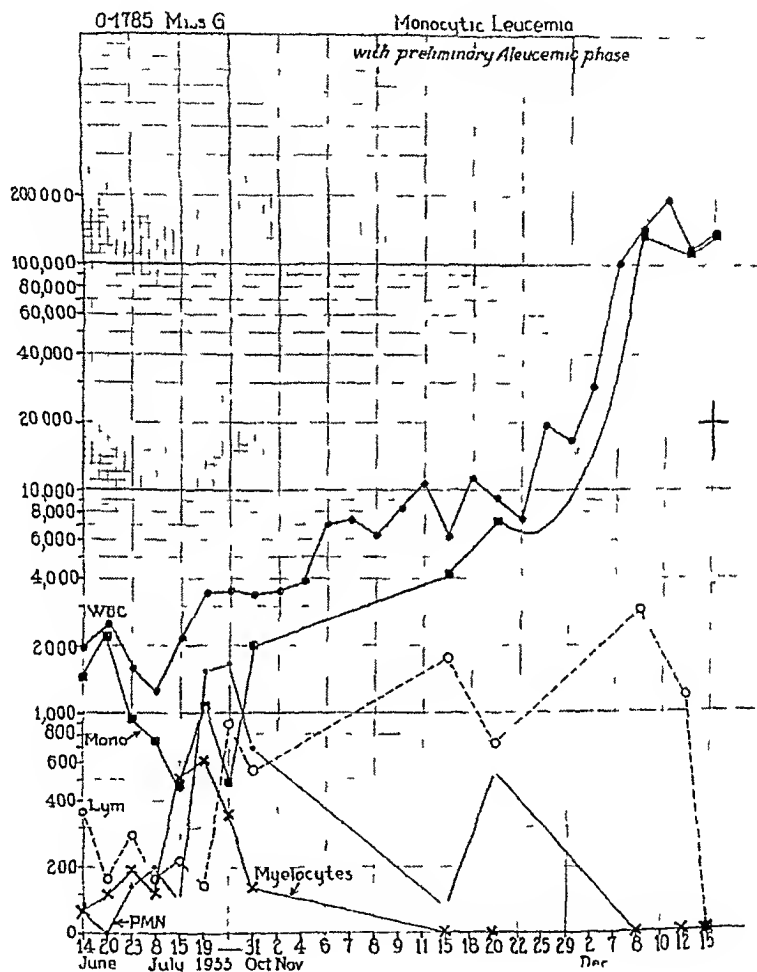


CHART 3 During the aleukemic as well as in the leukemic phase of this case the qualitatively changed and characteristic monocytes (see plate 3, figure 5) dominated the differential count. Myelocytes were present in the earlier months but disappeared as did most of the non-monocytic elements in the terminal stages of the disease, indicating extensive bone marrow invasion and replacement. The lymphocytes remained present longer and in more nearly normal total numbers than did the granulocytes.

degenerations (Plate 3, figure 5). Characteristic nuclear chromatin and cytoplasmic turbidity with azurophilic dust completed the identification. In the beginning myelocytes were present but as the peripheral count rose both mature neutrophils and myelocytes steadily decreased in relative and absolute numbers, the lymphocytes not so markedly.

It is important both from the standpoint of prognosis and of treatment to separate such cases as this one from the Schultz syndrome of agranulocytosis and from other leukopenic states,⁷⁰ and this may best be accomplished by an adequate qualitative study of the white cells

ACUTE MONOCYTIC LEUKEMIA

Our cases of fulminant monocytic leukemia have presented the typical acute manifestations with which the physician is beginning to be familiar, since the great majority of case reports now appearing in the medical literature deal with this striking symptomatic syndrome, which calls for immediate hospitalization and emergency measures

Case 6 G S, white female, aged 34 years, was first admitted to University Hospital, June 27, 1931 complaining of drowsiness, headache, fever (104° F) and photophobia, of one week's duration with a loss of eight pounds in weight during this period. Past history was entirely negative. Family history has no bearing upon this or the subsequent illness. Physical examination: temperature 99° F, pulse 88, respirations 20, blood pressure 118 systolic and 70 diastolic. The mouth showed considerable dental work but teeth and gums were in good condition. There was no lymphadenopathy. The thyroid gland was enlarged and nodular, especially on the right side. The chest, abdomen, and extremities were negative. The urine examination was negative, the Wassermann and Kahn tests negative, the basal metabolic rate minus seven. Total white cells, 11,250, differential-neutrophilic leukocytes 70 per cent, lymphocytes 29 per cent, monocytes 1 per cent, total red cells 4,520,000, hemoglobin 75 per cent (Dare). On discharge July 1, 1931 the diagnosis was acute upper respiratory infection, adenoma of thyroid, non-toxic.

On December 12, 1932, 17 months later, the patient again sought admission to the University Hospital with the complaint of severe oral infection. Early in November the patient had suffered from tonsillitis followed by an otitis media which had ruptured spontaneously and drained. In the middle of November gingival abscesses about the first and third upper molars were surgically drained. Before the end of the month she had had seven abscesses incised by her dentist. The oral involvement grew steadily worse until finally a medical consultation was advised.

The patient when admitted December 12 was obviously acutely ill. An extensive necrotizing process had invaded the left maxilla, practically all teeth both above and below appeared to be involved with a purulent gingivitis, and the breath was markedly offensive. The jaws could only be opened a fraction of an inch. The cervical nodes were greatly enlarged, painful and tender. At the time of admission she had been menstruating profusely for eight days and gave a history of 10 days of profuse hemorrhage following the onset of the previous menses (November 3). Frequent chills and fever had been experienced since the onset of the present illness with persistent nausea and on two occasions vomiting. The temperature on admission was 102.4° F. The following day the temperature reached 104° F, and for the most part this elevation (104° to 105°) was maintained throughout the course of the disease. The pulse ranged from 120 to 150, the respirations from 30 to 50. The blood pressure was 110 systolic and 58 diastolic. Moderate enlargement of the lymph nodes in all parts of the body was noted. The nodular cystic thyroid found on a previous admission was confirmed. The chest was essentially negative. The spleen was palpable and tender 6 cm below the left costal border, the liver was not palpable. There were no other palpable masses and no areas of tenderness. Reflexes and extremities were negative. The white count on admission was 99,000.

with 68 per cent young monocytes (plate 3, figure 4), 2 per cent monoblasts, 5 per cent mature active polymorphonuclears, 16 per cent myelocytes with none younger than the myelocyte "B" stage, 8 per cent small and 1 per cent intermediate sized

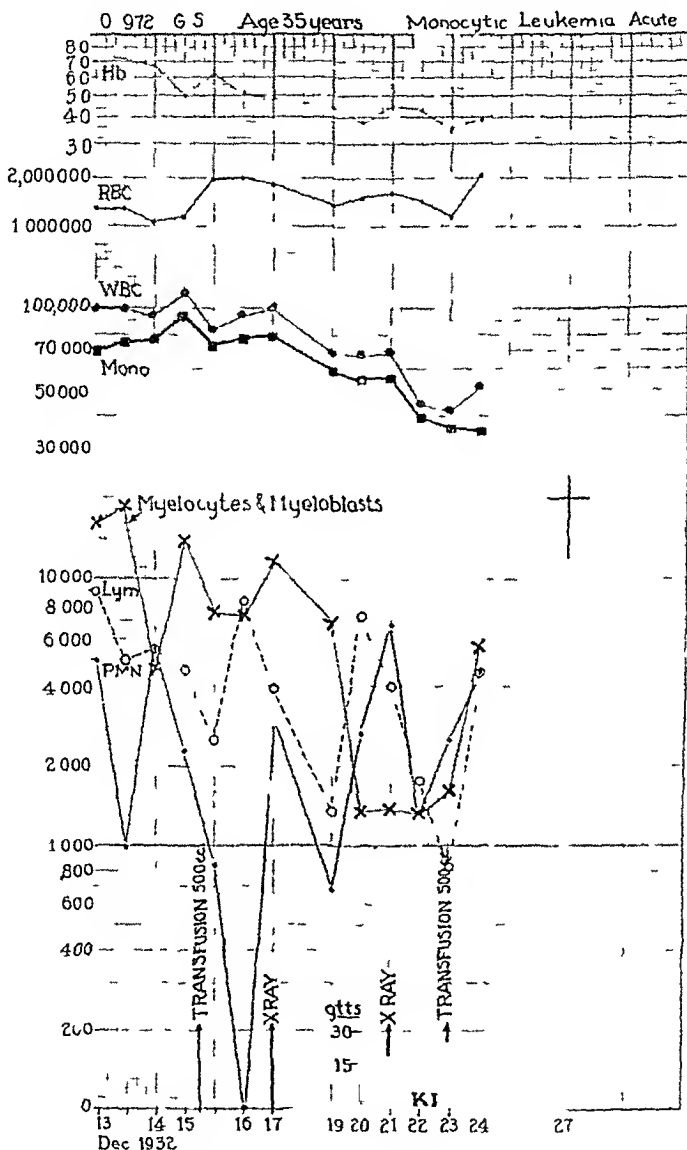


CHART 4 This graph depicts the blood findings in a patient with in acute, rapidly fatal, fulminant type of the disease, of six weeks' duration only, with monoblasts dominating the peripheral blood picture, 90,000 per cu mm, but with severe anemia and myeloblasts and myelocytes present to the extent of from 10,000 to 20,000 per cu mm, indicating progressive bone marrow invasion without complete replacement

lymphocytes See chart 4 for a summary of the blood findings in this case during the period of hospitalization. The total red cells were 1,310,000, hemoglobin 7.4 gm per 100 cc blood, erythrocyte hematocrit 13, leukocyte packed cell volume 9,

erythrocyte sedimentation 75 mm in 1 hour, fragility 0.471 to 0.300, icterus index 10, Wassermann negative, blood group, type IV Blood sugar 38 mg per 100 cc blood, NPN 40 mg, uric acid 11.1 mg Blood iodine 90 gammas % (normal 12)

Treatment consisted of two blood transfusions on December 15 and December 23 respectively, of two deep roentgen-ray exposures over the splenic area on December 17 and December 21, and of repeated large quantities of glucose-Ringer's solution intravenously Death occurred on December 27, approximately six weeks from the first onset of symptoms referable to the leukemia

Autopsy was performed December 28 by Dr Harry Rinehart, Pathologist to the University Hospital The anatomical diagnosis included acute, diffuse, necrotizing, semi-membranous gingivitis, pharyngitis, tonsillitis, hemorrhagic cellulitis of the left cheek, bilateral diffuse, nodular thyroid with cystic degeneration and hemorrhage, acute suppurative cervical adenitis, generalized adenopathy of moderate degree, bilateral bronchopneumonia, parenchymatous degeneration of the heart, enlargement of the liver, splenomegaly, acute ulcerative colitis, pigmented areas of old hemorrhage in mucous membrane of ileum and cecum, recent hemorrhage in urinary bladder, chronic adhesive perimetritis lacerations of the cervix, bilateral acute parenchymatous nephritis, bone marrow from humerus, femur, tibia, sternum, ribs, vertebra had the "gross appearance of that found in myelogenous leukemia", edema of the meninges of the brain

Microscopic examination revealed *Bone Marrow* The marrow everywhere was cellular, of a mottled gray color with very few normal appearing red areas Supravital studies revealed practically complete absence of fat and of erythropoietic foci, and but one or two granular cells were found in each oil immersion field A very rare megakaryocyte was seen The hyperplasia was found to comprise chiefly medium sized mononuclear cells with large vesicular nuclei and a finely mottled cytoplasm, many mitotic figures reflecting the rapidity of the growth Multinucleated cells were frequently encountered containing from two to five nuclei, not unlike the Dorothy Reed-Sternberg cells of Hodgkin's disease The multinucleated cells were of the same type as the predominating mononuclear cells and the entire group were distinctly foreign to the normal cytology of bone marrow Cover slip preparations of emulsions of marrow from humerus and tibia in autogenous blood plasma, stained with Wright's-Giemsa, confirmed the monocytic character of these cells Fixed sections further established the identity of the cellular response in the marrow with that of the circulating monocytic cells of the blood (Plate 2, figures 5 and 9)

Lymph Nodes Fixed sections from the inguinal, iliac, lumbar, retroperitoneal, mesenteric, mediastinal, axillary and cervical nodes were studied An atrophic thymus did not partake of the monocytic hyperplasia found elsewhere in lymphatic tissue Hemorrhage was commonly encountered The follicles were markedly atrophic with germinal centers either entirely absent or infiltrated with the large mononuclear elements, which also filled the sinuses Monocytic mitoses and eosinophilic granulocytes were prominent *Spleen* Weight 650 grams red, soft, smooth capsule, on cut section uniform reddish brown color with decided increase in pulp substance and an absence of visible Malpighian bodies The architecture was markedly altered by the overgrowth of monocytic cells, which had invaded the lymph follicles and which filled the dilated sinuses, occasional myelocytes and clasmotocytes, many mitotic figures were found in the monocytic cells *Liver* Weight 2350 grams, extended 5 cm below the costal border, showed parenchymatous degeneration, some focal mononuclear aggregations, and sinuses filled with monocytes *Lungs* Bronchopneumonia, edema with increased monocytes in alveolar septa and vessels, no evidence of tuberculosis *Heart* Weight 325 grams No monocytic accumulations in tissue other than those within vessels Moderate parenchymatous degeneration *Pancreas* and *adrenal* normal *Kidneys* Monocytic infiltrations with

definite scarring and tubular degenerations, glomerular tufts and capillaries showed abundant monocytic cells. *Stomach, duodenum, jejunum and ileum* showed evidence of old and recent punctate hemorrhages, the colon was the seat of definite ulcerative necrotic lesions with polynuclear and monocytic infiltrations. The *brain* showed only an intravascular increase of monocytes without tissue increase.

In brief, as was to be expected, all organs and tissues showed the intravascular increase of monocytic cells, and in addition, in those places where connective tissue reticular "mesenchymal rests" exist normally, loosely organized foci of characteristically disoriented monocytic elements were found, proliferating wildly as judged from the numerous mitotic figures, and more or less completely displacing normal structures. Bone marrow, lymph nodes and spleen, the principal sites for blood cell generation, present the most marked pathologic changes in monocytic leukemia, thus serving to demonstrate still further the close relationship which exists between the three types of white blood cells and the possibility of a common ancestry.

Case 7 D M, a white boy, aged five years, referred by Dr A G Helmick, was admitted to the Research Service of the University Hospital November 2, 1933, complaining of increasing weakness, pallor and swollen glands. On September 5, 1933 the patient complained of sore throat and suffered a gastric upset. One week later definite cervical adenopathy was observed. During the following month the cervical nodes fluctuated from time to time in size. About the end of September the patient developed a severe upper respiratory infection with secondary sinus involvement. An increasing disinclination to normal activity, increasing pallor, persistent adenopathy and the development of mouth breathing led to the diagnosis of tonsils and adenoids. Fortunately, prior to operative interference a routine blood study was requested and the following report returned: PMN 3 per cent, lymphocytes 97 per cent, hemoglobin 30 per cent. It was at this point that we first saw the patient. Bleeding from the nose difficult to control had occurred on two occasions and oozing from the gums was becoming increasingly troublesome. Spontaneous subcutaneous hemorrhages had appeared in addition to a recently noted increased susceptibility to bruises.

The past and family histories were unessential.

On physical examination the patient revealed temperature 100° F, pulse 128, respirations 28, blood pressure 104 systolic and 50 diastolic. The outstanding points were pallor, marked cervical adenopathy and a noisy type of mouth breathing. He was restless, active, but tired easily. Discolored areas were noted scattered over the entire body, the nail beds showed some cyanosis and the lips were dry and encrusted with dried blood. The conjunctivae were pale, but the eyes and eye grounds showed no hemorrhages. The nasal passages were occluded by excessive pharyngeal lymphoid hyperplasia, there was a posterior nasopharyngeal drip producing a gurgling type of mouth breathing, and necessitating frequent coughing, the tonsils were greatly hypertrophied with reddened pillars and small faucial isthmus. The gums were edematous, bleeding easily, and several small blood clots were seen about the teeth. A very fetid and offensive breath was apparent. On the dorsum of the posterior third of the tongue were two small hemorrhagic ulcers. The cervical nodes were prominent, firm, discrete, freely movable, not adherent to the skin, of variable size and slightly tender, the nodes at the angle of the mandible were largest, the submaxillary slightly smaller, those in the anterior triangle smaller than those in the posterior. The axillary nodes were about 2 cm in diameter, the epitrochlears and inguinals were also readily palpable. The chest was negative. The spleen

was enlarged, firm, extending 4 cm below the costal margin in the nipple line, but the liver margin was not definitely palpated. Genitalia, extremities and reflexes were normal.

Laboratory findings Total white count 20,600, supravital differential PMN 5 per cent, PMB 7 per cent, PME 5 per cent, myelocytes 10 per cent, small lymphocytes, 19 per cent, monocytes 49 per cent, monoblasts, 5 per cent. Blood platelets 6000 per cu mm. Total red cells 760,000 hemoglobin 34 gm per 100 c.c. blood, reticulocytes 32 per cent, hematocrit 9 erythrocyte fragility 0.412 to 0.300. The basal metabolic rate was plus 13. The sequence of events as reflected in the blood studies and the therapeutic measures employed may be followed from chart 5. Blood transfusion was performed as an emergency measure on admission and was repeated as often as was necessary during the succeeding weeks to control the hemorrhagic tendencies and provide a maintenance supply of red cells while attempts were being made to reduce the condition to a more chronic stage. Following the ineffectiveness of arsenic medication, roentgen-ray treatments were instituted and either a spontaneous exacerbation of the disease occurred or the irradiation actually accentuated the process. The total white count increased, the spleen and lymph nodes continued to enlarge, subcutaneous skin nodules appeared, and within one month death occurred. A postmortem examination was refused.

Myelocytes of the A, B, and C type were present at all times and an occasional myeloblast was encountered, but no irregularity in the division figures or in the symmetry of the nuclei and nucleoli characteristic of leukemic states was found. The lymphocytes were entirely within the qualitative range of normal at all times also, and the final exacerbation was reflected almost entirely in an increase in the monocytic elements.

THE PROBLEM OF MIXED LEUKEMIA

It will have been noted that in each of the cases cited in this series there have been recorded "shifts to the left" in both lymphoid and myeloid series. Nevertheless qualitative as well as quantitative data have been presented which suggest, and in four of the cases postmortem studies have confirmed, the primary incrimination of the monocyte rather than the other cell strains. Our remaining cases of monocytic leukosis have presented an even more striking mixture of cell types in the peripheral circulation, and undoubtedly represent the type of case which has been discussed in the literature as mixed leukemia. Certain pertinent data have been accumulated, however, which lead us to question a sound underlying pathologic basis for this clinical diagnosis. A mixed leukemia in which all three strains of white cells are equally involved is, of course, theoretically possible though unlikely, if our present concepts of their common stem cell origin are correct (diagram 1). It is only in so-called monocytic leukemia that we have encountered this liberal sprinkling of myelocytes and young lymphocytes, together with a monocytosis. In the classic myeloid or lymphoid syndrome the monocyte is never present in increased numbers, nor does it show peculiar qualitative changes, and usually the cell strain principally involved represents 95 to 99 per cent of all cells found in the blood. In the cases in which an equal quantitative distribution of the three strains of white cells has occurred in the blood with immature elements present from

each, it has been possible, nevertheless, by applying the criteria now available for the appraisal of normal cellular development, as contrasted with abnormal and disordered maturation, to distinguish the primary from the secondary involvement

We have illustrated elsewhere¹⁴ the amitotic nuclear division occurring in the myeloid elements in subacute myeloblastic leukemia. In this series the same asymmetry and atypical cellular division were noted in the monocytes. All of the cellular elements in the circulation showed some mitotic activity in the cases of monocytic leukemia. It was only among the monocytes, however, that we noted unequal division of nucleoli and asymmetrical distribution of nuclear chromatin, incomplete mitotic spindles with resulting nuclei of unequal size. Both myelocytes and young lymphocytes divided normally and the resulting multinucleated cells contained symmetrical and equally divided nucleoli. At postmortem the wide dissemination of monocytic hyperplasia, particularly at the sites and at the expense of myeloid and lymphoid generation, further confirmed the interpretation of primary monocyte pathology implied from the studies of the peripheral blood. These points will be presented in detail elsewhere and represent a distinct contribution which we believe the study of monocytic leukemia can make to a better understanding of the fundamental metabolic or environmentally conditioned constitutional disturbances upon which the leukemic states are engrafted.

ETIOLOGIC CONSIDERATIONS

Although the nature of the disorder, which permits or causes leukemic hyperplasia of monocytes, is not known, the mechanism of monocytosis in other pathologic states is more apparent. In general, the existence of either or both of two circumstances has resulted in a stimulation to monocytic proliferation: (1) the opportunity or need for phagocytosis of non-pyogenic bacteria or of other particulate matter, (2) the presence of an excess of lipoidal substances, occasioned either by certain disorders in the normal metabolism of fats, or by the liberation *in vivo*, or the parenteral introduction, of foreign monocytogenic lipoids.

We have already cited instances in which the phagocytic function of this cell strain has formed the basis for increased activity, and the clear cut results obtained in the studies with tuberculo-phosphatid immediately suggest the monocytogenic potentialities of other lipoids. Conversely, the cellular reactions in certain diseases known to involve disturbances in lipid metabolism appear to be largely of monocytic origin, though the evidence for strict cytologic identity is as yet inconclusive in some.

In certain cases of diabetic coma with lipemia, large foam cells not unlike hypertrophied monocytes may be found in the spleen and to a lesser extent in the lymph nodes, tissues normally the site of origin for monocytes. Of particular interest and probably of importance in considering this aspect of the problem is the apparent relationship of faulty lipid metabolism to

monocytic proliferation as observed in the so-called xanthomatoses. In Niemann-Pick's disease large phagocytic cells storing lecithin and phosphatid and arising from the reticulum cells⁷¹ are not only disseminated widely throughout the body in enormous numbers but may be found invading the blood stream. Whether this phenomenon is the result of a need for increased phagocytic function as suggested by Bloom⁷² or represents a specific stimulus from the blood lipid as suggested by the work on tuberculo-phosphatid and lecithin² is uncertain. A similar origin for the increased numbers of phagocytic cells noted in Hand-Schuller-Christian's disease is probable, the lipid deposition and lipemia consisting chiefly of cholesterol-fatty esters⁷³. The accumulation of fat-laden phagocytes in this disease forms a very characteristic granulation tissue which is readily converted into fibrous tissue, often causing severe anemia when it occurs in the bone marrow. The mechanism is not unlike that observed in Hodgkin's disease. In Gaucher's disease a lipemia consisting of the cerebroside, kersin⁷⁴ results in the formation of lipid storage cells in the tissues which are often multinucleated in type and suggest morphologically the giant cells of tuberculosis and Hodgkin's disease. In the monocytes of monocytic leukemia itself we have noted, as have others, the frequency with which vacuolar, fatty (?) degeneration is seen (plate 3, figure 5) in marked contradistinction to its occurrence in the cells in other types of leukemia.

Thus, tuberculosis, Niemann-Pick's disease, the Schuller-Christian syndrome, Gaucher's, and Hodgkin's disease, while differing clinically and pathologically, nevertheless have certain features in common. A generalized adenopathy with splenomegaly characterize the last four and may be present in tuberculosis. The development of granulomatous tissue with scar formation has been a common finding, more particularly in tuberculosis, Christian's disease and Hodgkin's disease. Large mononuclear, and multinucleated giant cells occur, being especially prominent in tuberculosis, Hodgkin's disease and Gaucher's disease. Some form of lipid disturbance has been shown to be present in each of these conditions except Hodgkin's disease, and in each, phagocytic cells probably of the monocytic strain, have reflected the major cellular response.

In typical Hodgkin's disease the characteristic blood picture includes an absolute, as well as a relative, monocytosis, together with a leukopenia, lymphopenia, eosinophilia, and anemia, the reversed monocyte-lymphocyte ratio reflecting the hyperplasia of monocytes and fibroblasts in lymph nodes and frequently in bone marrow. The etiology is as yet unproved, but if the avian tubercle bacillus or other acid fast organism is involved, as has been suggested,⁷⁵⁻⁷⁶ the lipid basis for the cellular pathology would be clear here also. Hodgkin's disease provides an interesting transition between the group of diseases showing monocytosis and the group of pathologic states which may be said to be leukemic in nature. The histopathology of lymph nodes and spleen from our cases diagnosed as monocytic leukemia (especially Case 1) was indistinguishable from that of typical Hodgkin's

disease. Subsequently we have found an instance in the literature⁵² of Hodgkin's disease reported as terminating in monocytic leukemia. Dame-shak⁷⁷ has noted the similarity between, and possible common etiology of so-called aleukemic reticulosis and Hodgkin's disease. It would seem that any approach to an understanding of the cellular reaction in Hodgkin's disease, the xanthomatoses and monocytic leukemia should be made with a full recognition of the basic studies on the mechanism of monocytosis in other diseases, more particularly those in tuberculosis with tuberculo-lipoids. This, of course, does not deny the possible neoplastic nature of some members of this group, but it does suggest an explanation of some of the features found in these diseases difficult to reconcile with the theory of malignancy.

DISCUSSION

In any study involving the cells of the blood and the organs and tissues from which they arise, the principal difficulty commonly encountered at the present time is the adequate differentiation of the mononuclear elements. Under pathologic conditions a "shift to the left" in any or all of the cell strains complicates the picture still further, with monoblast, myeloblast and lymphoblast presenting a minimum of criteria for differential identification. In plate 3 may be seen the transitional stages in the maturation from monoblast to mature monocyte as observed with the Wright's-Giemsa staining technic in the blood of patients with monocytic leukemia. The monoblast embodies characteristics which after careful study by comparison and contrast with myeloblast and lymphoblast usually make for its definite recognition. The density of the basophilia of the cytoplasm (plate 3, figures 1, 2, 3) is midway between that encountered in the lymphoblast and the lighter blue of the myeloblast. Usually one nucleolus, never more than two spherical nucleoli, are found in the characteristic, purple staining, splotchy chromatin of the monocyte nucleus. Figure 2 is typically representative of the gradual reduction in basophilia of the cytoplasm, which occurs during the early stages of maturation, to a maintained, opaque, mottled, cytoplasmic background within which appear many fine, scattered azurophilic granules in the mature state. Multiple nuclei (figure 4) are frequently encountered and in most of the leukemic cases there are from few to many highly vacuolated cells among the monocytes (figure 5). In the more chronic states many of the monocytes are qualitatively entirely normal (figure 6). The monocytes in the peroxidase stain react positively but usually may be distinguished from the granulocytes in the amount and distribution of oxidase granules. In the supravital studies with neutral red and Janus green, which always should accompany and supplement the fixed film surveys, the characteristic surface film motility, scattered fine blue-green mitochondria and a rosette of neutral red vacuoles identify the monocyte. These finer cytological differentiations are not apparent upon superficial casual examination, but with experience become increasingly de-

pendable. The experimental studies in tuberculosis formed the basis for the first careful analysis of the life cycle of the monocyte, revealing the epithelioid "shift to the right" in that disease. The study of monocytic leukemia provides the material for a similar appraisal of the maturation phases in this strain of cells with variable degrees of "shift to the left" toward the monoblastic level revealed.

In those cases which have come to autopsy in our series we have studied the various tissues carefully in an attempt to ascertain the origin and nature of the new growth of cells responsible for the abnormal blood picture. Always the principal sites of cellular hyperplasia have been in lymphoid tissue, spleen, liver and bone marrow. Arising diffusely in intervascular areas the characteristic large mononuclear monocytes have been found scattered loosely between and more or less completely displacing the normal cells. Many mitotic figures may be found, and deeply indented vesicular nuclei, frequently multiple and of varying size within the same cell (plates 1 and 2), serve to produce a cytological picture in the tissues altogether different from that seen in either myeloid or lymphatic leukemia. Studies of normal monocytic differentiation in the spleen¹³ and peripheral lymph nodes¹⁴ and of pathologic proliferation in experimental tuberculosis or after the injection of the lipid fractions from tubercle bacilli² have revealed the potentialities of latent connective tissue elements for monocytic differentiation when the proper stimuli are present. Fibrous connective tissue may also increase somewhat at times and the similarity between the pathologic tissue in monocytic leukemia and that found in Hodgkin's disease for example has at times been startling. The study of the five cases of monocytic leukemia coming to autopsy has served to reaffirm the evidence of the mesenchymal connective tissue origin of the monocyte adduced in the long series of studies already referred to in which this cell has been subjected to careful analysis. The fact that the monocytic hyperplasia in the leukemia of that type has occurred predominantly in those locations where the other white cell elements, myelocytes and lymphocytes, normally differentiate, further suggests the close relationship which we believe exists between the three strains of white cells in their earliest beginnings.

We have cited the wide range of clinical manifestations observed in our series of cases of monocytic leukemia, and the marked difference in acuteness and severity of the disease. This is of course, in conformity with the observed facts in the other leukemic states and in disease in general. Either the etiologic factor varies in its severity or in the duration of its effect upon the tissues or, as seems more likely, the constitutional reaction of the individual provides the conditioning factor which determines in the last analysis whether the pathologic trend is to be rapidly progressive or relatively quiescent. Each patient must therefore be studied quite objectively and from other standpoints than the blood picture, before an intelligent prognosis may be given. Just where the dividing line between a so-called benign, idiopathic monocytosis and chronic monocytic leukemia

should be drawn is not always clear, but the benefit of the doubt should be given the patient as long as the diagnosis of leukemia carries with it the implications of a fatal malignancy

SUMMARY

1 Clinical studies are aiding, and in turn are being distinctly furthered by a proper evaluation of the monocyte

2 The monocyte is an independent entity, with life cycle and functions specific to its own peculiar endowments

3 In tuberculosis the monocyte has been shown to reflect, and to be an important part of, the cellular reactions to the acid fast bacilli and more particularly to the lipoids elaborated by this group of organisms. When properly appraised and interpreted in conjunction with the other cellular elements of the blood and in the further light of available clinical and laboratory data, prognosis in this disease and an accurate prompt estimation of the effectiveness of any given therapeutic measure become possible

4 In Hodgkin's disease, syphilis, pneumonia, the xanthomatoses and in other pathologic states the monocyte if properly evaluated may contribute to the diagnosis of the disease and to the management of the patient

5 During the past four years 12 cases of monocytic leukemia have been diagnosed and nine have been carefully studied clinically with five post-mortem surveys

6 The problem of differentiating the leukemias and more particularly the question of mixed leukemia has been discussed and data submitted upon which to base judgment in the critical analysis of the individual patient

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REMARKS ON THE DIAGNOSIS OF CORONARY OCCLUSION *

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ABOUT eight or ten years ago, at a time when I was much interested in the clinical manifestations of coronary occlusion, I was often asked to see patients with symptoms of collapse following a severe attack of pain in the chest and under these circumstances had the satisfaction of pointing out how clearly and simply the diagnosis of coronary occlusion could be made. However, these opportunities have come very, very rarely during the past few years. At the present day the humblest practitioner of medicine and the most recent graduate are so thoroughly familiar with the clinical picture of this tragic event and so acutely alive to its recognition that the opinion of a consultant is seldom needed to suggest the diagnosis. Indeed, the diagnosis is frequently and readily proposed and having passed through the earlier period when it was seldom even thought of, I am now often surprised by being asked to see patients with coronary occlusion who are really suffering from some other disorder. It is astonishing how rapidly information about the condition has spread through the profession and with what eagerness and enthusiasm the knowledge has been applied. Now, when almost every sudden, severe pain in the chest of a person past middle life is at once called coronary occlusion, seems the appropriate time to sound a warning. There are other diseases of the heart, lungs and abdominal organs which may so closely resemble coronary occlusion that they are often distinguishable from it only with great difficulty and sometimes not until autopsy discloses the real state of affairs. It is not my purpose to discuss in detail the differential diagnosis of coronary occlusion. I wish only to dwell upon five conditions which in my experience have occasionally been confused with it. These conditions are upper abdominal disease, pericarditis, pulmonary embolism, rupture of the aorta and interstitial emphysema of the lungs.

I UPPER ABDOMINAL DISEASE

The diagnostic difficulty of distinguishing between coronary occlusion and upper abdominal disease is often very great. In spite of the fact that the similarity between the two conditions is generally well known the difficulty arises again and again. Sometimes the course of events quickly dispels uncertainty but at other times it is almost impossible to make a confident decision. The matter has been so often and so widely discussed that no more is necessary than briefly to mention it. On four occasions the difficulty has greatly puzzled me.

On one, the patient was operated upon for what was thought to be a perforated peptic ulcer. The peritoneal cavity and abdominal organs were

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found to be normal. Later a period of auricular fibrillation, the transient appearance of a pericardial friction rub and the occurrence of pulmonary embolism established the correct diagnosis.

On another, gall-stone colic with infection of the bile passages and gall-bladder was accepted as the explanation for pain, fever, leukocytosis and a slightly swollen, tender liver. Only weeks later was the error corrected when the unmistakable signs of beginning myocardial insufficiency appeared.

On still another, a prominent surgeon, called to see a man with intense upper abdominal pain, decided the symptoms were due to coronary occlusion not to gall-stones and asked a physician to take charge of the situation. However, two days later the patient was deeply jaundiced.

On the fourth, surgeons and physicians argued pro and con for two days, when finally the characteristic symptoms of coronary occlusion appeared.

II PERICARDITIS

Pericarditis may come on with sudden severe pain and the pain be quickly followed by the symptoms of myocardial insufficiency. Under these circumstances the severe pain, the pericardial friction, the fever and leukocytosis, the shortness of breath, the cyanosis, the congestive failure may simulate the manifestations of coronary occlusion. Again and again this diagnosis is made when patients with pericarditis are first brought into the hospital. On two occasions I have been consulted by young men under 40 who have told me that a diagnosis of coronary occlusion had been made a year or two before on the evidence of severe pain coming on abruptly and accompanied by a pericardial friction, fever, shortness of breath and certain abnormalities in the electrocardiogram. After recovery from this illness they had remained perfectly well and had had no symptoms whatsoever referable to the circulatory system. The examination at the time of their visit to me failed to disclose the slightest sign of any abnormality about the heart or circulation. I cannot cease wondering if they may have had pericarditis and not coronary occlusion. I add a brief summary of a few illustrative cases.

CASE I

A colored laborer, 29 years of age, entered The Johns Hopkins Hospital on June 15, 1933, complaining of severe pain over the heart. For a number of years he had been very obese, weighing as much as 240 pounds. The gain in weight had come on rather quickly about seven years before. During a year and a half before his admission to the hospital he had been treated in the Orthopedic Clinic for genu valgus and flat feet.

At four o'clock on the afternoon of the day before his admission the patient was awakened from a nap by excruciating pain beneath the upper end of the sternum. He sat upon the edge of the bed gasping for breath and moaning with pain. His misery continued unabated during that night and during the whole of the next day. In the evening he was persuaded to enter the hospital.

Examination Temperature 102° F, pulse 120, respirations 48, blood pressure 112 systolic and 50 diastolic

The patient was an obese young colored man. He lay propped up in bed with a moderate amount of dyspnea, complaining of intense pain over the heart. The least movement greatly increased the pain. Breathing was rapid and shallow. Obviously he was very ill. There was no cyanosis, no cough. The eyes were normally prominent. The pupils were equal and reacted actively. The eye movements were normal. The fundi showed no noteworthy abnormality. The nasal septum was perforated. The teeth were in very poor condition and there was marked pyorrhea. The tonsils were large and small patches of white exudate were seen on the left tonsil. The glands at the angle of the jaw were palpable, otherwise there was no glandular enlargement. The thyroid was normal in size. The trachea was in the midline, there was no tracheal tug. The chest was well formed and symmetrical. Over the bases of both lungs there were dullness, diminution in the intensity of the breath sounds and many moist râles. These signs were more marked on the left side than on the right except that the râles were much more numerous on the right. Over the heart there was a faint rippling pulsation in the fourth and fifth interspaces. The apex beat could not be seen or felt. The area of cardiac dullness was greatly enlarged and had a somewhat globular contour. Dullness extended 5 cm to the right and 12 cm to the left of the midline. The sounds were distant and faint. A soft systolic murmur was heard at the apex. The second pulmonic sound was accentuated. There was gallop rhythm. A loud to-and-fro pericardial friction was heard all over the heart. The pulse was regular, soft, not paradoxical. The peripheral vessels were not thickened. The abdomen was prominent and obese. Examination of the abdomen was difficult with the patient in a sitting position. There was no ascites. The liver seemed to be somewhat enlarged, the edge indefinitely felt 3 cm below the costal margin. There was minimal pitting edema over the shins. The neurological examination was negative.

Course in the Hospital The patient was desperately ill on admission and although from time to time there seemed to be a little improvement in his condition, the course was downhill. He died on the twelfth day after entering the hospital. During this period he always was very drowsy. He complained little but always had pain over the heart which was much increased by breathing and by changing posture. The area of cardiac dullness steadily increased so that at the time of death it was much larger than when he entered the hospital, the area measuring 6 cm to the right and 16 cm to the left of the midline. How much of the dullness was due to enlargement of the heart and how much to pericardial thickening and effusion it was impossible to say. There never was more than the slightest edema. The liver was not greatly enlarged, extending only a little below the costal margin. The lung signs increased in extent. At first there were the signs of fluid in both pleural cavities, later there seemed to be in addition evidence of consolidation particularly in the right lower lobe. Four attempts were made to tap the pericardium from different positions. The attempts made over the heart all failed to yield fluid. Two punctures in the left axillary area yielded a small amount of fluid, on each occasion about 150 cc. However, one could not be certain that this fluid came from the pericardial sac because there was fluid in the left pleural cavity. The fluid from the first successful tap was hemorrhagic, the cell count being red blood corpuscles 300,000, leukocytes 770. The second successful tap gave a turbid, yellow fluid of specific gravity 1.021, containing 10 grams of albumin per liter. The cell count was red blood cells 220,000, leukocytes 3200. A differential count of the leukocytes showed 62 per cent polymorphonuclears, 35 per cent lymphocytes and 3 per cent monocytes. The right pleural cavity was tapped on June 21 and 50 cc of fluid were removed. The patient finally became very weak with extraordinarily rapid, panting breathing and on June 27 he was found dead in

bed On admission the pulse was rapid and regular, later it was rapid and totally irregular, and shortly before death it again became regular

In this patient the sudden severe pain followed at once by the symptoms of myocardial insufficiency aroused the suspicion that he might have coronary occlusion or rupture of the aorta with the formation of a dissecting aneurysm After a few days of observation it was apparent that he had pericarditis On the wards it was thought that he had tuberculous pericarditis, but autopsy demonstrated that it was rheumatic

The anatomical diagnosis reads as follows Rheumatic vegetations on mitral and aortic valves, rheumatic scarring of mitral, aortic and tricuspid valves, scarring of myocardium, cardiac hypertrophy, acute rheumatic pericarditis, bilateral sero-fibrinous pleurisy, pulmonary edema, thrombosis of a branch of the pulmonary artery right upper lobe, slight lobular pneumonia, chronic passive congestion of lungs and liver, acute splenic tumor, diffuse scarring of pancreas and testes, beginning arteriosclerosis, obesity

CASE II

A colored laborer, then 37 years of age, came to the Medical Clinic of the Out-Patient Department of The Johns Hopkins Hospital on December 8, 1926, complaining of a cold which he had had for a week The physical examination on that occasion showed no important abnormality The heart was normal in size, the sounds perfectly clear The impression was expressed that the patient had an acute upper respiratory infection A roentgenogram of the chest showed the lungs to be clear The Wassermann reaction on the blood serum was strongly positive, and the patient was referred to the Syphilis Clinic for treatment He was reexamined in that department a few days later and once more the lungs and heart were found to be normal

On June 8, 1933, the patient entered the hospital complaining of pain in the chest which had come on the previous day He was in the hospital for one month with a characteristic mild attack of lobar pneumonia involving the left lower lobe and due to the pneumococcus Type IV Throughout the period of his stay in the hospital the heart was totally irregular He had been a patient at Mercy Hospital in December 1932 A letter from that hospital states that he had had lobar pneumonia of the left lower lobe At that time also the heart was fibrillating The cause for the auricular fibrillation gave rise to much speculation Some thought that in spite of the fact that the heart was little if any enlarged and the sounds perfectly clear, that he might have rheumatic mitral valve disease However, opinions favored the view that the disturbance of rhythm was associated with arteriosclerotic heart disease

The patient was admitted to the hospital again on January 2, 1934 After his discharge on July 8, 1933, he was reasonably well but he did not feel as well as he had before He came to the Syphilis Clinic from time to time where he was treated for the luetic infection Off and on he worked at odd jobs but felt unable to work regularly There was some shortness of breath on exertion During this period physical examination and roentgenograms demonstrated the persistence of infection in the lower lobe of the left lung One week before the second admission to the hospital, while working in the market moving heavy barrels, he was suddenly taken with severe pain in the interscapular area The pain was so intense that he had to stop work and go home He began to cough, the cough was worse at night and he was unable to sleep on account of the severity of the pain He grew more and more short of breath Two days before entering the hospital the pain shifted from the back to the front of the chest and was particularly severe over the lower end of the sternum The pain, he said, was exceedingly sharp, as severe as a *gothache*

Examination Temperature 100.2° F, pulse 104, respirations 24, blood pressure 108 systolic and 54 diastolic

The patient was propped up in bed complaining of severe pain about the heart. He was a short man, a typical chondrodystrophic dwarf. His pain seemed to be quite severe. There was only a moderate degree of dyspnea. Over the left shoulder was the scar of a stab wound received years before. The eyes were normally prominent. The pupils were a little irregular and constricted due to the administration of morphia. Later examinations demonstrated that they reacted actively to light and on accommodation. The eye movements were normal. The fundi showed a moderate degree of arteriosclerosis. In the left eye there was partial detachment of the retina. Many teeth had been extracted, those remaining were in poor condition. The throat showed nothing remarkable. There was no enlargement of the superficial lymph nodes. The thyroid was not enlarged. Over the lower lobe of the left lung the percussion note was impaired, the breath sounds were enfeebled, and a small number of scattered rales were heard after cough. The heart was enlarged. Cardiac dullness measured 5 cm. to the right and 12 cm. to the left of the midline. The apex beat was easily felt. The heart sounds were clear, the second pulmonic louder than the second aortic. A loud pericardial friction rub was heard over the heart, loudest in the fourth interspace. The area of dullness over the manubrium was somewhat increased. The rhythm was totally irregular. The peripheral vessels showed a moderate degree of arteriosclerosis. The abdomen was normal in appearance. No masses were felt. The liver and spleen were not enlarged. The genitalia showed nothing abnormal. There was no edema. The neurological examination was negative.

In this patient the situation was confusing. He had been fibrillating for over a year and it was assumed that he had arteriosclerotic heart disease. The sudden onset of pain followed by fever, leukocytosis, the symptoms of myocardial insufficiency and a pericardial friction suggested that he might have coronary occlusion. After a few days the signs of pericardial effusion developed and aspiration yielded a purulent fluid from which pneumococcus Type IV was cultivated. The pericardial sac was opened and drained. For a while the patient improved but later grew worse again and died two months after entering the hospital.

The anatomical diagnosis reads: History of pneumonia followed by pericarditis, dense pleural adhesions, left lower lobe, adherent thickened pericardium with drained walled-off pericarditis, mycotic aneurysm of arch of aorta extending into pericardium, generalized pleural adhesions, hypertrophy of right ventricle, chronic passive congestion of viscera, thrombosis in old caseous primary focus, right lower lobe, encapsulated caseous area in peribronchial nodes.

In both of these patients a very loud pericardial friction was heard over the whole heart. This is precisely what is usually heard with pericarditis and it is an important point distinguishing it from coronary occlusion. When a pericardial friction appears over an infarcted area of heart muscle it is a faint rub often difficult to hear, well localized and transient. I have never heard a diffuse, loud friction with coronary occlusion.

III PULMONARY EMBOLISM

In 1927 I published an article calling attention to the very great importance of embolic phenomena in the diagnosis of coronary occlusion.

I pointed out that pulmonary embolism occurred frequently and cited an instance illustrating how very, very difficult it may be to distinguish between coronary occlusion and pulmonary embolism. On account of its great interest in this connection I report the case again.

CASE III

A woman, 69 years of age, was operated upon by Dr. E. H. Richardson at the Hospital for the Women of Maryland and a perineal repair performed. She had been carefully examined a few weeks before by Dr. H. M. Thomas, Jr., who found no important abnormality, except that the blood pressure was systolic 160 mm Hg and diastolic 80 mm Hg. After the operation, convalescence progressed uneventfully, and on the twelfth day the patient was out of bed. On the evening of the fifteenth day, while walking about the corridor, she suddenly had a feeling of faintness and would have fallen had she not been supported by a nurse. When she had been gotten to bed she complained of a feeling of pressure over the chest and difficulty in getting her breath. The following morning she still complained of constriction in the chest and shortness of breath.

The blood pressure was much lower than it had been before operation, but no estimate had been made after operation. The pulse rate, previously around 80, rose to 100 and over and remained thereabout. The heart was a little further out to the left. The patient had a grayish, slightly cyanotic color, was deeply prostrated, and gave one the impression of being seriously ill. The following afternoon a definite coarse, to-and-fro pericardial friction was heard over the sternum and to the left of it, which disappeared after six or eight hours and did not return. The lungs remained clear except for a few râles at the base, and there was no cough and no bloody expectoration.

For a week or longer the patient remained prostrated, was delirious and displayed Cheyne-Stokes breathing. On the twenty-seventh day after operation, swelling of the left leg with pain in the groin pointed clearly to thrombosis of the left femoral vein. The swelling of the leg subsided, the delirium cleared, the pulse slowed and the patient gradually improved. In September she was out of bed and she left the hospital September 24 in good condition.

At the time I thought the patient had had coronary occlusion but even then I was perplexed and uncertain, as shown by the comments I added. "It was my own belief, shared by Dr. Thomas, that the patient had had a coronary occlusion. The character of the attack, the appearance of the patient, the rapid pulse, the fall in blood pressure, the pericardial friction together make a convincing picture. Hearing about the illness without an opportunity to see the patient, one might well argue for pulmonary embolism. The time after the operation, the sudden onset, the symptoms of shock, the left femoral thrombosis, all strongly suggest pulmonary embolism. It might even be suggested that the rub heard over the heart may have been a pleuro-pericardial friction. I am convinced it was not. However, it is not my intention to argue the point but rather to illustrate how difficult at times the diagnosis may be."

It is certainly true that the symptoms and the course of events during the illness were typically characteristic of postoperative thrombophlebitis with pulmonary embolism and no other diagnosis would have been considered.

had it not been for the presence of a pericardial friction Does the appearance of a pericardial friction make it necessary to abandon the diagnosis of pulmonary embolism with infarction when all the other symptoms are typical of the condition? This question troubled me continuously until the observation of a second somewhat similar instance convinced me that a loud pericardial friction may occur with infarction of the lower lobe of the left lung under circumstances when the possibility of the occurrence of coronary occlusion is very remote, if not indeed beyond all reasonable expectation

I shall not now pause to discuss whether the pericardial friction was an endopericardial or an extrapericardial rub It seems to me likely that it was extrapericardial All I can say with certainty is that it was a very loud to-and-fro friction and that from the character of the sounds it was impossible to decide whether it was endo- or extrapericardial The main facts about this second case are as follows

CASE IV

A clergyman, 43 years of age, entered the Bon Secours Hospital under the care of Dr E D Freeman, on May 5, 1932 During the previous year and a half he had had recurring attacks of severe upper abdominal pain which Dr Freeman diagnosed gall-stone colic Under conservative treatment there was no improvement, indeed, the attacks became more frequent and more severe The patient was a rather obese man, in good general condition, who showed no abnormality on physical examination other than tenderness in the epigastrium and in the gall-bladder area The blood pressure was 132 systolic and 78 diastolic On May 19, 1932, the patient was operated upon by Dr E H Hayward and the gall-bladder removed The diagnosis made at operation was chronic perforation of the gall-bladder, chronic cholecystitis and hepatitis adjacent to the gall-bladder Dr H S Everett examined the tissues removed at operation and reported subacute cholecystitis and cholelithiasis

During the first week after operation the patient progressed satisfactorily From time to time he had a little asthmatic wheezing He had had asthma since 16 years of age, particularly in the spring and early fall Everything went well until the morning of May 25 when he was suddenly taken with severe pain in the left axilla and left shoulder The temperature which during the previous week had fluctuated between 98° and 100° rose to 102° and the pulse rate to 120 Later on the same day a pleural friction rub was heard in the left axillary area The patient was somewhat shocked and a little cyanotic The following four or five days he had cough with frankly bloody expectoration The symptoms were very characteristic of pulmonary embolism and this diagnosis was made The patient then steadily improved during the week until June 2 On that day when turning on the left side, he suddenly went into a condition of collapse There was great shortness of breath, he became pale and cyanotic and the pulse rate rose to 130 The following morning a loud to-and-fro friction was heard all over the heart The manifestations on this occasion, though somewhat more severe, were exactly like those which had occurred a week before, except that there was no pain and the symptoms of collapse were followed by the appearance of a loud pericardial friction The presence of the precordial friction led to the suspicion that this attack might be one of coronary occlusion With this diagnosis in mind, Dr Freeman asked me to see the patient

At the time of my visit, which was about 32 hours after the onset of the symptoms of collapse, the patient still was very ill, he was propped up in bed quite dyspneic, very pale, somewhat cyanotic and sweating profusely It was impossible

to make a thorough examination. However, there were definite signs of consolidation in the left axilla and in this area also a pleural friction. All over the heart there was a loud grating to-and-fro friction. There was no variation in the intensity of the rub with inspiration. The pulse was rapid, of small excursion and the pressure was low.

From then on the patient steadily improved. At the end of four days the pericardial rub had disappeared and after that he made a slow but otherwise uneventful recovery. He left the hospital on July 5, 1932.

After leaving the hospital when he began to walk about he noticed that there was some swelling of the left calf, the left calf measured two or three centimeters more than the right calf. He wore a pressure bandage and the swelling soon disappeared.

On March 3, 1934, I had an opportunity to examine the patient again. He said he had been perfectly well since leaving the hospital and had had no symptoms except a little irritation in the throat and a little wheezy cough from time to time. These asthmatic symptoms, however, had been much less severe than they had been in former years. There had been no symptoms whatsoever referable to the heart or circulation. No pain about the heart, no palpitation, no shortness of breath, no symptoms which might to the slightest degree suggest angina pectoris. The examination on this occasion was entirely negative except that the patient had gained some weight and was moderately obese. The notes of the examination are as follows:

Examination Temperature 98.2° F, pulse 72, respirations 16, blood pressure 132 systolic and 80 diastolic. Weight 188 pounds. Height 5 ft 7¼ inches.

The patient is somewhat obese, 32 pounds above the average weight for his height and age. He has a good color and a healthy appearance. He is a mouth-breather. The eyes are normally prominent, pupils equal, react actively, eye movements are all normal. The teeth are in good condition. The tongue is clean. The throat shows no abnormality. There is no enlargement of the superficial lymph nodes. The thyroid is just felt, average size, symmetrical, no nodules. The chest is well formed and symmetrical, with a wide costal angle. Movements are equal on the two sides. The lungs are perfectly clear except for a slight degree of emphysema. The apex beat of the heart is a barely visible impulse in the fifth interspace inside the nipple line. The area of cardiac dullness is not enlarged. There is no impairment over the manubrium. Heart sounds are clear and of normal quality. Pulse is regular, the peripheral vessels not thickened. The abdomen is normal in appearance. In the right upper quadrant is the scar of the operation wound. There is a fairly thick panniculus. No tenderness. No masses are felt. The liver and spleen are not enlarged. There is a little prominence of some of the superficial veins about the left ankle. At the present time no swelling of the left leg. The measurements about the calves are 38 cm. on each leg.

IV RUPTURE OF THE AORTA

When this Society met at Baltimore two years ago I demonstrated at Ward Rounds a patient showing all of the classical manifestations of coronary occlusion. The following day a distinguished Visiting Physician selected the patient to illustrate his remarks upon the same subject. At the time no one doubted the accuracy of the diagnosis. I shall briefly state the main facts about the case and tell the subsequent developments.

CASE V

A white married housewife 63 years of age, was admitted to The Johns Hopkins Hospital on November 27, 1930, complaining of intense pain under the sternum and

shortness of breath For four or five years she had had dyspnea on exertion and occasionally a feeling of substernal pressure with dyspnea which would pass after a short period of rest Two days before admission, while varnishing a piece of furniture, she suddenly was seized with intense pain in the region of the heart She described this sensation saying it felt "as though the insides were being torn out" again "as though there were an expanding ball inside the chest about to burst," and yet again "as though she had been hit by a sledge hammer" She fell back dazed, perhaps even unconscious, and was carried to bed The pain continued, not so severe as at first, but still very severe, and a hypodermic injection administered by a physician gave but little relief She vomited a number of times and had some cough with slightly blood-streaked expectoration She was brought to the hospital 53 hours after the onset of symptoms

Examination Temperature 102° F, pulse 108, respirations 34, blood pressure 210 systolic and 140 diastolic

The patient was a rather obese woman, highly flushed, breathing rapidly and complaining of substernal pain There was moderate cyanosis The eyes were normally prominent, pupils equal, reacted actively The eye grounds showed moderate arteriosclerotic changes The teeth had been extracted and she wore a complete double denture No enlargement of the superficial lymph nodes The thyroid was not enlarged The lungs showed no abnormality other than the presence of numerous moist râles over both lower lobes The heart was enlarged, sounds much enfeebled There was a faint systolic murmur at the apex The sounds at the base could scarcely be heard The pulse was regular except for an occasional extrasystole The abdomen was soft and relaxed No tenderness Liver and spleen not enlarged Slight pitting edema over the shins The pelvic and rectal examinations revealed nothing abnormal

Course During First Stay in the Hospital The patient was given morphia, was then bled and digitalis started She continued to have severe attacks of substernal pain The blood pressure, which on admission was 210 systolic and 140 diastolic, fell rapidly to 110 systolic and 78 diastolic then slowly rose again during the following twelve hours to 180 systolic and 70 diastolic The temperature was 99° the following day and thereafter only occasionally a little elevated The leukocytes varied from 9,000 to 16,000 during the first week The patient's general condition, which was desperate on admission, improved a little but she continued to be miserable, with frequent attacks of substernal pain and severe attacks of coughing associated with urgent dyspnea The pulse, regular on admission, was totally irregular the following day and fibrillation continued from that time Paravertebral injections of the sympathetic ramus somewhat relieved the pain but did not abolish it The physical examination showed but little change during the period of her stay in the hospital The heart sounds became more forcible There was a great deal of discussion about a diastolic murmur, which some heard but which others could not hear Sometimes this murmur was heard only at the apex, at other times faintly to the left of the sternum The patient left the hospital April 15, 1931, still in a rather miserable and unsatisfactory state

Interval Note At home she was always miserable She could make no effort and only with assistance could take a few steps from chair to chair On July 6, 1931, she was seen in the Dispensary when she was very short of breath and cyanotic Examination otherwise did not differ from what had been found when she was in the hospital Later in July she began to have still more severe attacks of pain and the cough became more troublesome In October she began to have a different type of pain from that which she had had before This consisted of attacks of severe, sharp pain in the epigastrium, and from then on this symptom remained more prominent than any other Patient was admitted to the hospital again on November 20, 1931

Examination Temperature 99.4° F, pulse 88, respirations 26, blood pressure 150 systolic and 95 diastolic

The patient was propped up in bed, with marked dyspnea. Evidently she had lost a great deal of weight. There was moderate cyanosis. She complained bitterly of severe pain about the heart and gnawing pain in the epigastrium. Occasional attacks of cough occurred with severe dyspnea. The face was quite drawn and contracted with pain. Skin and mucous membranes had a fairly good color. The eyes showed nothing abnormal. There was no enlargement of the superficial lymph nodes. The thyroid was not enlarged. The lungs were clear except for numerous moist râles over both lower lobes and a few scattered sonorous râles. The heart was enlarged, the area of dullness measuring 5 cm. to the right and 12 cm. to left of the midline. At the apex the first sound was loud and booming and was followed by a loud, blowing systolic murmur. In the aortic area there was a rough systolic murmur, and the aortic second sound was accentuated and somewhat ringing in quality. The pulse was totally irregular, peripheral vessels thickened and tortuous. The abdomen was soft and relaxed. Marked tenderness was present in the epigastrium, particularly over the aorta. The aorta could easily be felt. It seemed to be wider than normal and to pulsate violently. No clubbing of the fingers was noted and no edema of the legs. The neurological examination was negative.

Course After admission the patient improved very little. She was constantly most miserable, with substernal pain, attacks of coughing with intense dyspnea, and complaining always of a severe gnawing pain in the epigastrium which varied a good deal in intensity. In some of the attacks of dyspnea there was wheezing. Everyone agreed that the abdominal aorta was dilated and tender and some thought there was a fusiform dilatation. On this admission, as on the first, there was a dispute about a diastolic murmur. At times the patient was delirious. On February 22 she contracted the respiratory infection then prevalent on the Ward. She developed bronchopneumonia and on February 27, 1932, was released by death from all her misery and suffering.

The blood count demonstrated a mild secondary anemia. The Wassermann reaction on the blood serum was negative. The urine contained albumin and a few casts. The temperature on the first admission was 102°, it fell rapidly to normal and thereafter varied at first from 97° to 99°, occasionally going to 100°. During the second admission it varied from 97.6° to 100°. Later it fell to normal and with the terminal pneumonia rose and varied from 99.6° to 104°.

Many electrocardiograms were taken. In all there was evidence of myocardial disease but the curves did not show the changes characteristic of coronary occlusion.

Roentgenograms showed enlargement of the heart and aorta. The measurements of the teleroentgenogram were M R 6, M L 10.4, T 27.2.

The anatomical diagnosis reads Arterio- and arteriolosclerosis, scarring of kidneys, atrophy of acinar tissues of pancreas, history of hypertension and auricular fibrillation, cardiac hypertrophy and dilatation, focal necroses and scars in myocardium, chronic passive congestion of viscera, bilateral hydrothorax, subcutaneous edema, dissecting aneurysm of aorta and iliac arteries, saccular aneurysm of dissecting aneurysm, fibrous adhesions between right auricle, arch of the aorta and pericardium, chronic bronchitis and tracheitis, emphysema, lobular pneumonia, chronic cervicitis and retention cysts in uterus, myomata and polypi uteri, secondary anemia, hyperplasia of bone-marrow.

During the past three years I have encountered seven instances of rupture of the aorta at clinical pathological conferences. In all seven the diagnosis of coronary occlusion had been made when the patient first entered the hospital but in five it was changed to rupture of the aorta before

the autopsy findings were disclosed. When the patient dies shortly after the accident occurs the distinction between the two may be very difficult as the following case illustrates.

CASE VI

A white man, 79 years of age, was brought to The Johns Hopkins Hospital on November 12, 1929, in an unconscious state. He had always been in remarkably good health except that for some time he had been somewhat short of breath on exertion and occasionally had had a little substernal pain especially at night. About 10 o'clock on the morning of November 12 as he was riding home from work on the street car, he was suddenly seized with severe pain under the sternum. He became very dizzy and lost consciousness. He was picked up by the police and brought to the hospital. In the accident room he regained consciousness and could only state that he had had a very severe pain and had then lost consciousness. He was obviously deeply shocked and quite ill. He was a little short of breath, the hands and feet were cold, there was marked cyanosis and the pulse was imperceptible. The blood pressure could not be taken by auscultation, by palpation the systolic pressure was 58 mm Hg. He was at once admitted to the Ward.

Examination Temperature 98.7° F, pulse 76, respirations 24.

The patient was an old man with marked arteriosclerosis of the peripheral and retinal vessels. Respirations were somewhat labored. He complained of a dull aching under the sternum. The chest was narrow and thin, disproportionately wide antero-posteriorly. The lungs showed nothing remarkable except a few râles at the bases. The heart was somewhat enlarged, the area of dullness measuring 4 cm to the right and 11½ cm to the left of the midline. The apex impulse was in the seventh interspace, the action irregular due to the occurrence of numerous extrasystoles. The first sound at the apex was followed by a short systolic murmur. The sounds were feeble and could not be heard at the base. The abdomen showed nothing remarkable except that the liver was felt 5 cm below the costal margin.

Course in the Hospital After stimulation, the patient's condition at first improved somewhat. The blood pressure in the right arm rose to 174 systolic and 130 diastolic. The pulse was never more than vaguely perceptible. Following the accident he remained anuric for 30 hours.

Two days after admission he suddenly developed abdominal distention, complained of abdominal pain and soon afterward died, apparently of cardiac failure. Shortly before death there was a little dullness at the right base suggesting the presence of a patch of pneumonia.

Laboratory Examinations Blood count Hemoglobin 74 per cent, red blood corpuscles 3,740,000, leukocytes 11,560.

The leukocytes varied from 12,000 to 18,000. The Wassermann reaction on the blood serum was negative. The urine showed an abundance of albumin with many hyaline and granular casts. The nonprotein nitrogen and uric acid of the blood were at a normal level. The temperature on admission was normal and then gradually rose, varying irregularly between 99° and 101°.

Roentgenogram of the chest showed a soft infiltration at both apices, tuberculous in character. Electrocardiogram, rate approximately 94. Rhythm totally irregular. Slurring of R-waves in all leads, low voltage in all leads.

The anatomical diagnosis reads: Dissecting aneurysm of ascending aorta with rupture into pericardium, hemopericardium, arteriosclerosis, emphysema, bilateral multilocular hydrocele, thickening of splenic capsule, diverticulum of duodenum, minute abscess of liver.

In distinguishing between coronary occlusion and rupture of the aorta too much reliance must not be put upon the electrocardiogram. A man, 45 years of age, was suddenly seized while eating his mid-day meal with excruciating pain in the chest radiating to the left shoulder. He died at the end of 24 hours and the autopsy revealed rupture of the aorta with the formation of a dissecting aneurysm. The electrocardiographic report reads as follows: P-waves of low voltage. QRS slightly slurred. Q-waves prominent in Lead III. T-waves inverted in Lead I, diphasic and of low voltage in Lead II, upright in Lead III.

Comment Record suggests coronary artery disease.

V INTERSTITIAL EMPHYSEMA OF THE LUNGS

CASE VII

On February 12, 1933, I saw at Washington with Dr. W. C. Moore and Dr. J. W. Esler, a physician, 51 years of age, who had previously enjoyed excellent health. On the morning of February 8 while shaving he was suddenly seized with intense pain in the region of the heart radiating to the left shoulder. The pain lasted about half an hour and then gradually passed. When Dr. Moore examined him two hours later no definite abnormality was found. The heart and lungs were quite normal. The temperature was 98°, pulse 54 and regular, respirations 20, blood pressure, systolic 110 and diastolic 80. The following day an electrocardiogram was reported by Dr. Esler as follows: Regular rhythm, rate 60, T-waves upright in all leads, conduction interval normal, maximum QRS potential 9 mm. The blood count was normal, the leukocytes 8,550 per cubic mm. On the morning of February 11 the patient reported to Dr. Moore that during the night when lying on the left side he had heard a curious loud bubbling, crackling sound synchronous with the heart beat. His wife sitting on the bed beside him could easily hear the sound. At this time Dr. Moore could make out no abnormality whatsoever on physical examination. The heart and lungs were quite normal. The temperature was 98°, pulse 66, respirations 20, blood pressure, systolic 100, diastolic 75.

Later in the day Dr. Esler thought he heard a pericardial friction. This seemed to establish the diagnosis of coronary occlusion which had previously been suggested. When I saw the patient on the afternoon of the following day he was sitting up in bed laughing and talking, protesting that he felt perfectly well. He certainly was in good spirits and had every appearance of robust health. The temperature, pulse, respirations and blood pressure were all normal as they had been before. I examined the heart and the lungs with the greatest care and could detect nothing that was to the least degree abnormal. When I expressed surprise the patient laughingly said that he could easily produce the sound. He turned on his left side, shifted about a few moments and suddenly said, "There it is." I put my stethoscope over the apex beat of the heart and with each impulse heard the most amazing sound. It is difficult to describe. Crunching is the best adjective I can think of though it is far from apt especially since crunching has been widely used to describe pleural friction to which it bore no resemblance. It certainly conveyed the impression of air being churned or squeezed about in the tissues. It recalled an instance of pneumopericardium I had listened to years before. When the patient turned on his back the sound at once disappeared. The possibility of pneumothorax came to my mind. However, a second thorough examination of the lungs was quite negative. Still I persisted and suggested that it might be a small localized pneumothorax near the apex of the heart. The following day a roentgenogram was taken with a portable machine by Dr. E. M.

McPeak Dr McPeak's report reads as follows "Examination of the chest shows the bony thorax, heart and great vessels normal in appearance There is slight thickening of the interlobar pleura on the right side with some slight increase in density throughout the right base The appearance in the right base is probably due to bronchiectasis There is no other evidence of abnormality except perhaps a very slight widening of the aortic arch and the thoracic aorta"

The extraordinary sound disappeared after a few days At the end of two weeks the patient was up and about and during the past year has led an active life and has had no symptoms of ill health Dr Moore examined him on February 20, 1934, and found him in excellent condition

The course of events in this patient convinced me that he did not have coronary occlusion and yet I could not clearly understand what had caused the sudden pain and how the extraordinary sound heard over the heart had been produced I revolved the matter in my mind again and again until four months later when I saw in the wards of The Johns Hopkins Hospital a boy with subcutaneous emphysema in the neck and emphysema of the mediastinal tissues The moment I put my stethoscope over his heart it flashed upon me that here was the explanation for the puzzling sound I had heard over the heart of the Washington physician I add a brief account of the illness of this patient

CASE VIII

A white boy, 17 years of age, a tin worker, was admitted to The Johns Hopkins Hospital June 25, 1933, complaining of pain on breathing Though a delicate lad, he had previously always been well On the day before admission at 6 p m, while sitting quietly on a chair, he suddenly had a feeling of pressure under the sternum as though there were a lump there Soon swelling actually appeared above the clavicles and he had severe pain on breathing deeply, on swallowing and on turning the head He was seen in the accident room a few hours after the symptoms came on Examination of the throat and larynx revealed no abnormality There was subcutaneous emphysema of the tissues in the neck and over the upper part of the chest During the night he was very uncomfortable with pain under the sternum especially on deep breathing and swallowing He spent most of the night sitting up The next morning he entered the hospital

Examination Temperature 101.2° F, pulse 86, respirations 24, blood pressure 110 systolic and 70 diastolic

A thin, pale, undernourished boy lying quietly in bed complaining of pain under the sternum and about the neck He was mildly apprehensive There was subcutaneous crepitation over the front of the neck which extended backward to the trapezius muscle on both sides and downward over the clavicles to about the second rib on the left and the nipple on the right

The eyes were normally prominent, the pupils equal and reacted actively to light Extraocular movements were normal Slight enlargement of the superficial lymph nodes in neck, axillae and groins was present The thyroid was not enlarged The chest was long and thin with a narrow costal angle The sternum was prominent, producing a slight degree of pigeon breast The lungs were clear The apex beat of the heart was in the fifth interspace 6 cm to the left of the mid-line The sounds were distant, barely audible They were obscured by a loud systolic crunching sound heard all over the heart and in the left interscapular area behind The abdomen was normal in appearance Walls soft and relaxed No tenderness No mass Liver and spleen not enlarged Right kidney easily felt Reflexes normally active

Course after Admission to the Hospital The temperature which was 101.2° on admission gradually fell and after the third day was normal. The symptoms all soon subsided and the subcutaneous emphysema and curious sound over the heart disappeared. He left the hospital well 20 days after admission. On July 31, 1933, he reported at the Out-Patient Clinic. He was feeling perfectly well and the physical examination was quite negative.

Laboratory Examinations Blood hemoglobin 105 per cent, red blood cells 5,240,000, leukocytes 13,000

Wassermann reaction (blood), negative

Roentgenogram 6/26/33 Chest subcutaneous emphysema Free air in the tissues of the neck and trachea, free air in the mediastinum

7/5/33 Lungs clear

Urine Specific gravity 1.018, no albumin, no sugar, a few leukocytes in the sediment

It might be objected in this instance that the peculiar sounds heard over the heart may have been due to the pressure of the stethoscope upon air in the subcutaneous tissue of the chest wall since crepitus was felt below the left clavicle. However, I am convinced that the sounds could not have been produced in this way because they occurred only with each contraction of the heart. In the following case this possibility was entirely excluded as there was no subcutaneous emphysema of the chest wall.

CASE IX

A white maid, 24 years of age, came to the Out-Patient Department of The Johns Hopkins Hospital, May 31, 1930, complaining of pain in the abdomen and chest. She was examined first in the Gynecological Clinic where no important abnormality of the pelvic organs was discovered. She spoke of having spat blood now and again over a period of years. Examination in the Medical Clinic was quite negative. There was no abnormality about the heart or lungs and a roentgenogram of the chest showed the lungs to be clear. She was then referred to the Laryngological Clinic where infection of the left antrum was found. From then on she was treated in this clinic at intervals for years. The antrum was irrigated on a number of occasions. On June 18, 1931, the left ethmoidal cells were opened and drained. Five days later a radical operation was performed upon the left antrum. She recovered satisfactorily from the operations but continued to have headaches, unpleasant symptoms of nasal occlusion and a profuse purulent discharge. On the morning of July 17, 1933, the left antrum was irrigated. In the afternoon the left side of the face began to swell and the pain became more and more severe. In the evening the following note was made by Dr. James Bordley, Jr.: "Following irrigation of the left maxillary sinus the patient developed emphysema of the cheek. Late this evening she began to complain of pain about the heart accentuated by respiration. At present she is quite uncomfortable. Every now and then she sits forward with the hand pressed over the heart complaining of severe pain. When asked to localize the pain she places the finger just to the left of the sternum at the level of the sixth and seventh costal cartilages. There is no respiratory difficulty, no cyanosis, and no pain in the left shoulder or arm. Subcutaneous emphysema of left side of face is present and subcutaneous crackles extend down to the clavicles on both sides of neck. No emphysema is noted over the chest or in axillae. On auscultation over the heart there are numerous popping and crackling sounds which vary with the cardiac cycle and with respiration. The heart sounds are somewhat distant especially at the base of the heart. There is a resonant note over the manubrium. The lungs are clear. There is no evidence of pneumothorax. Impression: Emphysema of face, neck and mediastinum."

After four days the emphysema had completely disappeared and the patient was as well as before. There was slight fever during the attack, 98.6° to 100° . Leukocytes were 10,462.

Listening to a description of these episodes it may appear far fetched to say that they resemble the manifestations of coronary occlusion. However, under certain circumstances the resemblance may be very close. Not, it is true, when there is subcutaneous emphysema, but if the air escapes into the interstitial fibrous bands of the lung and travels only to the mediastinum then the similarity may be very confusing. With the escape of air and the tearing apart of the fibrous tissue there is sudden severe pain. This may be followed by fever and a slight leukocytosis. The systolic crunching sound which is heard over the heart may easily be mistaken for a pericardial friction. If the observer is not familiar with the peculiar symptoms which accompany this accident, coronary occlusion may be erroneously diagnosed.

HEPATIC FUNCTION IN RELATION TO HEPATIC PATHOLOGY EXPERIMENTAL OBSERVATIONS^{*}

By FRANK C MANN, M D , *Rochester, Minnesota*

It is the ideal and ambition of the investigator in experimental medicine to discover new facts by the experimental method in order to aid the clinician in his work of preventing disease and healing the sick. While I would object strenuously to the viewpoint that all experimental research should be practical in nature or have a practical aspect, because it is not possible to evaluate research in terms of practical application, nevertheless the experimental investigator with a clinical point of view strives to undertake to investigate those problems in which the answer may ultimately benefit the patient. This was the object which my associates and I had in mind when we undertook a series of investigations on the functions and experimental pathology of the liver. The results of our investigations have only partially fulfilled our hopes and must be considered at present as having accomplished little more than preparation for what we hope will be more fruitful investigations. A general review only will be presented since the scope of our subject is broad and the number of investigations we have made on it numerous.

The liver has many definite and important known functions. Knowledge of the physiologic activity of the liver, even though this activity is vital and manifold, has not been of great value to clinical medicine owing mainly to a lack of knowledge of how the hepatic functions are affected by pathologic changes in the organ. From the experimental standpoint, therefore, the next step, after determining some of the functions of the liver, was to investigate the effect of hepatic injury on these functions. This necessitated the experimental production of pathologic lesions of the liver and their study.

Many methods have been used to produce pathologic changes in the liver and to decrease hepatic function. These include (1) employment of the more or less specific hepatic poisons, as chloroform, phosphorus, carbon tetrachloride, and so forth, (2) partial removal of the organ, (3) obstruction of the biliary outflow, (4) shunting of the portal blood away from the organ, and other less used methods.

One fundamental characteristic of the liver usually has been responsible for defeating the purpose of most of the experiments performed in order to reduce the functional capacity of the liver. Restoration to some extent occurs in most organs of the body after partial removal or injury. It occurs to a very remarkable extent in the liver. This characteristic of the liver makes it difficult to produce experimentally a decrease in the functioning

^{*} Read at the Chicago meeting of the American College of Physicians, April 16, 1934
From the Division of Experimental Medicine, The Mayo Clinic

hepatic tissue to such an extent that the hope would be justified that the physiologic activity had been reduced to an amount that could be measured

The effect of hepatic poisons on the liver is usually transitory, and if the animal recovers from the acute effects of the drug, the hepatic parenchyma is restored to almost its normal condition. It is only by repeated administration of such substances that a more permanent pathologic change can be made in the liver. Although there are many substances which will produce a more or less specific hepatic injury, for purposes of experimental investigation carbon tetrachloride is the best so far discovered. As was shown by Lamson¹⁸ and his associates, repeated administration of this substance in appropriate doses for several weeks produces a condition of the liver similar to cirrhosis as seen in man.

Partial removal of the liver, from individuals of those species of animals in which removal is anatomically possible, produces a decrease in hepatic tissue but not for a very long time. Restoration of the normal organ, even after as much as 70 per cent has been removed, is usually rapid and complete^{14, 17}

Obstruction of the biliary outflow injures one function of the liver, that of secreting bile, but does not greatly interfere with the other hepatic functions or greatly injure the hepatic parenchyma unless the obstruction is maintained for several months. By that time the effect of the obstruction itself on the other tissues of the body is so great that it is hazardous to interpret the results of functional studies in terms of hepatic injury.

The shunting of the portal blood from the liver by an Eck fistula produces within a few weeks a decrease in the size of the liver by about one-half. This atrophy, however, usually is not of sufficient magnitude to be of value for studies of hepatic insufficiency. Our studies on animals with an Eck fistula have been disappointing.

We have found that a combination of these various methods furnishes a preparation in which functional hepatic tissue is permanently decreased. We discovered that restoration of the liver after partial removal either did not occur, or only to a limited extent, if (1) the portal blood was shunted away from the organ, (2) if biliary obstruction was present, or (3) if cirrhosis existed. If any one of these procedures was carried out, that is, making an Eck fistula, obstructing the common bile duct, or producing cirrhosis, and if a portion of the liver subsequently was removed, a definite and permanent decrease in hepatic tissue was secured²². It was sometimes possible to decrease the hepatic tissue to 15 per cent or less of the normal amount. The results of the investigation which we wish to report were secured from observations made in part on animals from which the liver had been totally removed, partially removed, injured transitorily with chloroform or phosphorus, or made cirrhotic with carbon tetrachloride. Other observations were made on animals from which the liver had been partially removed after an Eck fistula had been made, after obstruction of the biliary outflow, or after the development of cirrhosis.

In attempting to evaluate methods for estimating hepatic function, several facts concerning the functional characteristics of the liver should be constantly kept in mind (1) The capacity of the normal liver to carry on its many functions is greatly in excess of the normal needs of the organism. Although this statement is probably true of all organs of the body, it is particularly applicable to the liver. It would thus seem to be extremely difficult ever to measure the capacity of the normal liver in regard to any one of its functions without producing a very abnormal physiologic condition. (2) The capacity of the liver to perform its functions is dependent on many factors, and may change with extreme rapidity. Determination of a specific hepatic function of a particular animal at a definite time, even if it could be made with reasonable accuracy, would not necessarily be the same after a very short period of time. (3) A decrease in one of the functions of the liver does not necessarily mean that all functions, or any other one of its many functions, are equally impaired or even at all injured. There seems to be a dissociation of functions of the liver, so that it is possible for one to be defective in an otherwise normally functioning organ. (4) Most of the functions of the liver are so intimately associated and correlated with the physiologic activity of other organs or tissues that it is difficult or impossible definitely to delineate the hepatic factor. Hepatic activity is often only a part, although important and often vital, of a physiologic process in which one other organ or tissue, or more than one, is involved. (5) Finally it should be noted that the liver maintains all its known and therefore its possible measurable functions with extreme stubbornness. Normal hepatic functions are carried on by a very small amount of functioning tissue. An animal without a liver may be totally unable to maintain a certain physiologic process, while an animal with only a small percentage of its normal amount of hepatic tissue seemingly may function as well in this respect as when all its liver was present.

STUDIES OF THE BILE AND ITS CONSTITUENTS

The function of the liver which in the past has been of most interest to the clinician is secretion of bile. This is owing to the fact that the bile contains a pigment which, when retained in the body, excreted in the urine, or prevented from reaching the digestive tract, furnishes definite evidence to the clinician that something may be wrong with the function of the liver or the discharge of its external secretion. Study of this secretion is handicapped by the fact that it is poured into the intestine and is not readily accessible for observation. It has been necessary, in order to overcome this difficulty, to study the more important constituents of bile as they may be retained in the body or appear in the urine.

The bile contains several substances, three of which appear to be the most important: cholesterol, bilirubin, and bile acids. Too little is known at present in regard to cholesterol, either its origin or significance in the bile.

to justify a consideration of it as a possible indication of hepatic function even if it were possible to obtain the bile directly and to estimate the cholesterol quantitatively. Bilirubin and the bile salts have been important substances in the search for a method of estimating hepatic function.

Because jaundice was the first clinical sign observed of hepatic dysfunction, bilirubin has been in the past, and still is probably, the most important substance used to indicate hepatic injury. Physiologically several important facts are known concerning bilirubin which have important bearings on its employment as an indicator of hepatic function. These facts are (1) bilirubin is formed from hemoglobin²⁶, (2) a considerable portion of the bilirubin found in the bile is formed outside the liver^{21, 23, 24, 25}, (3) only a small portion of the normal liver is necessary to excrete all the bilirubin formed in the body²⁰, (4) only bilirubin which has reached the hepatic cells gives the so-called direct van den Bergh reaction⁷. Although satisfactory methods have been developed for estimating the amount of bilirubin retained in the blood, such as the van den Bergh method¹ and the icteric index,³⁰ and though the data so secured may be of great clinical value, the facts mentioned definitely indicate that such data do not suffice for quantitating hepatic injury, as the amount of bilirubin formed and the rate at which it forms depend on several factors, many of which determine or change the rate of formation of bilirubin and the amount of this substance formed. Probably the most important of these, which is not hepatic, is the amount of hemoglobin available for making bilirubin, and the amount of hemoglobin in turn depends on several factors, as destruction of blood, loss of blood, and diet.

Bollman and I⁹ have made attempts to determine whether we could correlate the amount of bilirubinemia with the amount of hepatic tissue present, or with the extent of hepatic injury. We found that the amount of bilirubin in the blood, as previously has been suggested, depends on many other factors than hepatic injury. For instance, an animal with obstruction to the biliary outflow will have a large amount of bilirubin in the blood a few days after the beginning of the obstruction, and at a time when the liver appears almost normal, and will have only a small amount of bilirubin in the blood several months after the obstruction, when the liver is very severely injured. An almost undetectable amount of bilirubin may be present in the blood of a dog the hepatic tissue of which consists of a single cirrhotic lobe, while intense jaundice will occur in a normal animal after administration of toluylendiamine, at a time when very little hepatic injury is demonstrable.

The bile salts appear to be products of activity of hepatic cells and to have at least one known function, that of assisting in the digestion of fat. Although no completely satisfactory methods are available for the determination of bile salts in body fluids, such methods as exist are sufficient to afford considerable information about the metabolism of these substances. Accurate methods for determination of bile salts in the bile have permitted Whipple³⁰ and his collaborators to draw the following conclusions from

their studies of animals with complete biliary fistulas. Daily excretion of bile salts is constant under constant dietary and physical conditions, dietary factors may affect the amount of bile salts formed, bile salts administered by vein or by mouth are rapidly and quantitatively excreted in the bile, the liver is probably responsible for the elaboration of bile salts, and slight hepatic injuries may greatly reduce the amount of bile salt formed and excreted. Bollman has modified the method of Gregory and Pascoe¹⁶ so that he has obtained fairly satisfactory results with the determination of bile salts in the urine and blood of dogs. He has made the following observation on the formation and determination of bile salts in normal animals, and on animals with different types and degrees of hepatic injury.³

The normal animal excretes only traces of bile salts in the urine, and bile salts are not definitely detectable in normal blood. Following intravenous administration of glycocholates or taurocholates only a small portion appears in the urine and the injected material rapidly disappears from the blood. Large amounts may be given by mouth without appearing in the blood, urine or feces. After complete removal of the liver, bile salts do not appear to be formed, but administered bile salts are quantitatively excreted in the urine within a few hours after injection. If biliary excretion is prevented by ligation of the biliary ducts, bile salts are excreted in the urine, but not all of the injected bile salts are recovered in the urine. It would appear that the liver plays a predominant part in destruction of bile salts as well as in their formation.

In the experiments with animals in which bile fistulas have been made, and with animals with complete obstructive jaundice, both formation and destruction of bile salts appear to be influenced by the condition of the liver. Excretion of bile salts in the urine in the presence of obstructive jaundice is definitely less than that in the bile in the presence of biliary fistulas. This appears to be due to the destruction of bile salts in the presence of obstructive jaundice, since administered bile salts are not all excreted, as they are in the presence of biliary fistula. Various agents which affect the liver reduce excretion of bile salts. Infection of the intrahepatic ducts, toluylendiamine, chloroform, carbon tetrachloride, or phosphorus poisoning may reduce excretion of bile salts to less than one-tenth of its former value. The greatest reduction occurs at the time of greatest hepatic injury, but marked reduction in excretion of bile salts may be obtained with hepatic injury too slight to be detected by ordinary histologic examination. The ability of the liver to destroy bile salts may not be altered, so that it would appear that the ability of the liver to form bile salts is easily impaired. Hepatic injury by toluylendiamine, carbon tetrachloride, or chloroform sufficient to give rise to urinary excretion of bile pigment, usually is accompanied by excretion of increased amounts of bile salts in the urine. If animals retain bile pigment in the blood from injury to the liver, or from uncomplicated biliary obstruction, increased amounts of bile salts may be found in their blood. Severe

hepatic injury reduces the amount of bile salts found in the blood, apparently by reducing the formation of these substances

A fairly accurate index of the condition of the livers of dogs with complete biliary obstruction was obtained by following the concentration of bile salts in the urine. The greater the excretion of bile salts under these conditions, the better has been the condition of the liver. Jaundice develops after a slight or moderate amount of hepatic injury, obstruction is associated with moderate excretion of bile salts. Improvement of the condition of the liver decreases the excretion of bile salts, but additional injury to the liver also diminishes excretion of bile salts. While the results of these observations would indicate that the concentrations of bile salts in the blood and urine are significant in postulating hepatic injury, it is questionable if such data can be used to quantitate hepatic function. The fact that the liver appears both to make and to destroy these substances would seem to preclude such a possibility.

THE USE OF DYES

The fact that the liver excretes many other substances, such as minerals and dyes, in the bile, has led to the common use of the rate of excretion of certain dyes as a method of estimating hepatic function. Since it is not the normal function of the liver to excrete these foreign substances, and since some of these tests are of clinical value, we believe they should not be called tests of hepatic function.

Most of our studies of dye methods for estimating hepatic function have been made by observing the rate of disappearance from the blood of an injected dye, such as bromsulphthalein or rose bengal. Many dyes may be used which appear to be specifically excreted by the liver. With a dose of dye that is entirely eliminated from the blood of normal animals in a few minutes, large amounts of the dye are found to be present in the blood several hours after injection into animals with complete biliary obstruction, or into animals from which the liver has been completely removed. Partial removal of the normal liver from animals, however, does not alter the excretion of dye in direct proportion to the amount of liver removed. If the remaining portion of liver is not injured by anesthesia or surgical trauma, little influence is noted after removal of more than half of the hepatic tissue, and a small amount of hepatic tissue (10 per cent) may take only twice as long to clear the blood of dye as is required by the liver of the normal animal. It should be emphasized that the remaining portion of liver of these animals is essentially normal, and that in all probability the normal hepatic cells do not become blocked by the dye but continue to pass it into the bile. In this way the fewer cells appear to be almost as efficient as a larger number working with a relatively smaller concentration of dye.

We have also attempted to correlate the results of dye tests with the amount of gross and microscopic pathologic change in the livers of animals

in various stages of cirrhosis caused by carbon tetrachloride. Specimens were immediately obtained at biopsy following completion of the dye test. It was immediately obvious that it was impossible to interpret the microscopic pathologic change in the liver from its gross appearance at exploratory laparotomy, particularly in the group of cases in which the liver appeared normal to gross examination, but had extensive microscopic changes. In general, the extent of pathologic change in the hepatic cells appeared to parallel the retention of the dye. The scirrhous changes in the liver apparently bore no relation to the excretion of dye. There were many exceptions, in which the results of dye tests failed to correspond to the pathologic change found in the liver. Some normal animals gave definite evidence of retention, and some animals with extensive gross and microscopic hepatic injury failed to retain any dye.

It would appear justifiable to conclude from these observations, in so far as the experimental animal is concerned, that the rate at which the liver removes a dye from the blood stream indicates how fast the liver will remove that particular dye from the blood stream at that time. When taken by itself it is not reliable in quantitating the extent of pathologic changes in the liver or how well the many other functions of the organ are being performed at the time the test was made. On the other hand, it may indicate hepatic injury and is probably as good a method as any developed to date for doing this.

ESTIMATES BASED ON CARBOHYDRATE METABOLISM

One of the most important functions of the liver has to do with carbohydrate metabolism. The liver is apparently either directly or indirectly responsible for maintaining the concentration of glucose in the blood. In this capacity it stores carbohydrate in the form of glycogen, which can readily be converted into glucose, and it can also make carbohydrate from proteins, and glucose from some of the other sugars. So many attempts have been made to measure hepatic function, and so many methods have been developed for it, based on this phase of hepatic activity, that it is impossible to review them adequately here.

Most of the tests concerning carbohydrate metabolism have been based on utilization of one of these sugars: dextrose, levulose, or galactose. All three are used in tolerance tests, and in addition, changes in the dextrose content of the blood following administration of drugs which produce hyperglycemia have been taken as criteria of hepatic function. Although it is true that hepatic activity is an important factor in removing an excess of dextrose from the animal organism and that there is a marked difference between the dextrose tolerance of a normal animal and that of a dehepatized animal,³² the fate of dextrose in the animal organism depends on so many extrahepatic factors that only under very special conditions could a change in glucose tolerance indicate impaired hepatic function. The use of a hyperglycemic agent to indicate hepatic injury is based on the facts that the liver

is the essential organ for producing hyperglycemia,^{19, 27} and usually an injured liver does not contain as much glycogen as the normal organ, therefore the hyperglycemia should be less in the presence of an injured liver. It should be noted that the glycogen content of the normal liver may vary within wide limits, from a minimum of less than 1 per cent to a maximum, as Butsch¹³ has shown, of more than 20 per cent. It can thus be seen that only under special conditions could this test be of significance. Bollman and I,⁹ using epinephrine as the agent for producing hyperglycemia, have attempted to use this test on our animals with reduced hepatic parenchyma, but have found it unreliable. However, it might be employed to advantage for specific purposes.

Although the liver does make glycogen from levulose, the muscles can do this also, and levulose can be utilized by an animal without a liver.⁶ Consequently, it is difficult to understand how a levulose tolerance test could be used to measure hepatic injury.

Theoretically it should be possible to indicate hepatic injury by a galactose tolerance test, as the utilization of this sugar appears to depend mainly on the liver.³³ However, as Millet³¹ has shown, the difficulty in employing this test experimentally is due to the wide difference in rate of utilization of galactose by the normal animal.

When all the known factors that enter into the metabolism of carbohydrate are considered—the rapidity with which it may be utilized by the normal animal and the slowness of its utilization by the fasted animal, its storage in large amounts in two major sites, liver and muscle, and the difference in the manner of utilization of the glycogen in these two sites, the enormous influence of insulin on it, the formation of fat from it, and when it is further recognized that there are probably many more factors to be discovered, as the recent work on the pituitary body and suprarenal gland would indicate, it would seem that the utilization of any phase of carbohydrate metabolism to measure hepatic activity, even though the liver has a major part in such metabolism, is almost hopeless. All the investigations on this problem made in our laboratory would tend to confirm this pessimistic outlook.

DETERMINATIONS BASED ON PROTEIN METABOLISM

The liver is essential for normal protein metabolism. Deamination,¹² formation of urea,^{5, 10} and oxidation of uric acid to allantoin^{8, 11} depend on the liver. None of these processes, when measured in the usual manner, occur in the dehepatized animal. On the other hand, an animal with greatly reduced hepatic parenchyma may carry on these processes at almost the same rate as the normal animal, with the exception of the formation of allantoin from uric acid.²⁰ The latter process is decreased by hepatic injury.¹

Green¹⁵ has studied the nitrogen partition in the blood and urine of dogs, when they were normal and after the development of various degrees of cirrhosis produced by carbon tetrachloride. He administered small quan-

tities of carbon tetrachloride to dogs, two or three times a week, for periods of from two to seven months. The animals were maintained under standard conditions and the total urinary excretion was analyzed daily for the main nitrogenous constituents. At various periods of time the nitrogenous constituents of the blood were also determined. From time to time the animals were etherized and the liver explored, its condition noted, and a specimen secured for histologic examination.

Definite lesions were produced in all of the animals. The lesions were progressive in nature, as was determined by exploration and histologic examination of the specimen secured. In the animals to which the drug was administered for several months, the liver became markedly cirrhotic.

During the production of the hepatic lesions, there were changes in both actual and relative amounts of nitrogenous constituents excreted in the urine. There was a decrease in the amount of urea, and an increase in the amount of ammonia, amino acids, and uric acid. Creatinine accounted for a fairly constant percentage of the total amount of nitrogen excreted. The most marked early changes were seen in the amount of amino acid excreted, which would almost double within a few days after beginning administration of the drug. Later, the amount of uric acid was the most altered, the increase amounting to several hundred per cent.

Our observations on the effect of hepatic injury on those phases of nitrogen metabolism in which the liver has been definitely proved to be involved, indicated that the hepatic injury cannot be quantitated by changes in excretion of the essential nitrogenous constituents. There remains, however, the possibility that a method of measuring hepatic function may be developed from utilizing one of its activities in relation to metabolism of nitrogen.

ESTIMATES DEPENDING ON SO-CALLED HEPATIC DETOXICATION

The liver usually has been considered as the site of destruction of many toxic substances. There is no question but that hepatic tissues will render inert many substances which are harmful to the organism. However, in only a limited number of instances has it been proved that the liver actually destroys the active agents. It is known that the liver is the site of destruction of almost all strychnine³⁴ that gains access to the body, and that it will destroy more nicotine² than all the other tissues of the body. On the other hand, it is not more active in causing epinephrine²⁸ and ephedrine³⁵ to disappear than the other tissues of the body. At present there is no method of determining whether the liver will destroy any given substance without direct experimentation. Adequate physiologic methods are at hand to determine whether the liver specifically destroys a substance, provided the substances under investigation can be estimated either biologically or chemically in the blood or tissues.

Many tests of hepatic function have been devised, based on the ability of the liver to destroy certain substances. In order to justify employment

of any substance for this purpose, it should first be demonstrated that the liver actually destroys all or a major portion of the substance, and it is necessary to have a method of quantitating the substance either directly or indirectly. Too often the sponsor of a given test has not troubled himself to fulfill both of these necessary requirements. There are very few tests, based on this phase of hepatic activity, in which it has been consistently proved that the test substance is actually destroyed in the liver.

Some very serious objections are encountered in attempting to measure the ability of the liver to destroy a given substance. Many of the substances so used are toxic to the liver or to the organism as a whole. This undesirable effect will be greatest in those instances in which the test is most desired, namely, where the hepatic parenchyma is reduced. The effect of the substance on the liver or organism often depends on the physiologic state of the liver at the time the substance was administered. The differences in effect of certain hepatic poisons on the glycogen-filled and glycogen-depleted liver is a good illustration. Furthermore, there may be a marked difference in the response to a given substance, depending on whether it is given when the subject is in a fasting or in a digesting state.

Owing to the considerations named we have not felt justified in using many of these tests in our investigations. Early in our work we discovered that although many of the substances used in an attempt to measure the capacity of the liver to destroy them would, in a given amount, be harmless to the normal dog, they might, in the same dose, cause severe reaction or death of animals with greatly reduced hepatic parenchyma. It should be noted, however, that there is a definite and possibly valuable field for investigators to discover a nontoxic substance, destroyed by the liver, which can be measured by some suitable method. At present such a substance does not appear to be available.

Numerous other supposed methods for measuring hepatic function have been described. Some of these tests are based on physiologic processes which have never been proved to be due to hepatic activity. Few of the tests, other than those previously given, appeared to have sufficient merit to justify investigations on experimental animals in our laboratory.

It should be noted that in our investigations we have taken the gross and histologic appearance of the liver as the standard for indicating the amount of hepatic injury. While we do not believe that such a standard is adequate, until a better one is developed it must suffice. For this reason I have confined this paper to a relation of our observations on attempts to correlate changes in known functions or activities of the liver in relation to the amount of hepatic tissue present or to the pathologic condition of the organ at the time the observations on function were made.

SUMMARY

A series of studies has been made to determine if a quantitative relationship could be found between the amount of apparently functioning

hepatic tissue and the capacity of such tissue to maintain any one of the many known functions of the liver. Methods were employed which would produce definite and permanent decrease in hepatic parenchyma. The amount of hepatic tissue possessed by the animals studied varied from normal to none and included a series of animals in which the hepatic injury was graduated from that in which the liver was severely injured acutely to that in which only a small amount of markedly cirrhotic hepatic tissue remained. Observations usually were made of the gross and microscopic appearance of the liver immediately after completion of each study of function.

Several important physiologic processes cease immediately after the liver is totally removed. Other processes are greatly modified. On the other hand, extreme reduction in hepatic parenchyma, as much reduction as it was possible to produce and have the animal survive, produced slight or no changes in those physiologic processes which were abolished or modified by total removal of the organ. The results of our studies would indicate that extreme caution must be used in attempting to postulate the pathologic condition of the liver of an individual by the results of the so-called hepatic function tests. In these studies none of the many methods for measuring hepatic functional capacity which we tried were wholly reliable in indicating to us the approximate extent of reduction of hepatic parenchyma, and injury to hepatic parenchyma, as determined by gross and microscopic observations made immediately after completion of the test. While several of the tests may be of value clinically, it would seem that unless their use is combined with other methods of determining hepatic disease they may cause serious error.

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BRONCHOSCOPY IN PULMONARY DISEASE

PRESENT STATUS AS AN AID IN DIAGNOSIS AND TREATMENT

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THE use of the bronchoscope as an aid in the diagnosis and treatment of diseases of the lung has been practically a development of the last decade. Before that time the bronchoscope was used chiefly for the removal of foreign bodies. The modern bronchoscopic technic, using the distally lighted tube of Jackson, without general anesthesia, has widened the field of its usefulness to such an extent that bronchoscopy is indicated in practically every disease of the lung, at some time during its course, in some particular patient. In modern bronchoscopy general anesthesia is not required. In acute inflammatory conditions of the lung, as well as in dyspnea produced by obstructive lesions, general anesthesia is contraindicated, and in these conditions bronchoscopy may be of the greatest aid both in diagnosis and treatment. When we speak of modern bronchoscopy we refer to the technic as originated by Dr. Chevalier Jackson, and as developed by him and his coworkers in the various bronchoscopic clinics in Philadelphia.

Personal course postgraduate teaching has created a world-wide interest in bronchoscopy. By intensive courses for special instruction in bronchoscopic technic and the clinical application of the procedure, established in one school, the Graduate School of Medicine of the University of Pennsylvania, 636 physicians from the United States have received preliminary training in cadaver and dog work and clinical instruction in bronchoscopy. These physicians have come from practically every large city in every state in the United States. There have come also 87 student physicians from 19 foreign countries and states, including Canada, the South American States, the British Isles, three Central European states, China, Japan, Australia, South Africa and New Zealand. These student physicians were for the most part well established otolaryngologists prior to their taking the work in bronchoscopy. With adequate equipment and a trained personnel they have carried on the work on their return home and many reports have come to us of the success of their work in bronchoscopy.

The aid rendered by bronchoscopy is so essential both in diagnosis and treatment that the time will come when a bronchoscopic clinic will be as much a part of a hospital that treats pulmonary diseases as is the roentgenologic department. Bronchoscopy will, however, always supplement roentgenology in the matter of diagnosis, because the function of the bronchoscope

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is to look into the lung and the function of the roentgen-ray is to look through it

Bronchoscopy as an Aid in Diagnosis The first bronchoscopic examination is essentially a diagnostic study and in every case will give findings supplementary to other methods of examination. The larynx, trachea and larger bronchi can be inspected without general anesthesia by the use of distally lighted instruments. They are made of such size that even the new-born infant can be examined¹ without trauma, if the proper technic is followed.

Among the points noted in the bronchoscopic examination may be mentioned the appearance of the bronchial mucosa, the quantity and character of secretion, evidence of abnormality of the lumen of the trachea and bronchi, evidence of abnormal mobility, fixation or deviation of the trachea and bronchi and, finally, a careful inspection of the bronchial movements during respiration and cough. The location and extent of the lesion as seen intrabronchially is of first importance. The origin of pus or abnormal secretions from a branch bronchus gives an indication of the lesion in the area of lung supplied by the branch bronchus in question. The relative quantity of air that is passing in and out may be roughly estimated. The presence of bronchial dilatation, compression stenosis, intrabronchial lesion, growths, ulceration or infiltration can be readily determined. The significance of bronchoscopic findings should be interpreted with a knowledge of the findings obtained by the internist on physical examination and the results of roentgenologic studies. The removal of secretions uncontaminated by mouth organisms, and of specimens of tissue for biopsy, where the appearance of the local lesion in the opinion of the bronchoscopist justifies it, will give positive information that cannot be obtained by any procedure other than bronchoscopy.

Bronchoscopy for Treatment The purpose of bronchoscopic treatment is to establish and maintain a functionally normal airway throughout the tracheobronchial tree so that there may be a state of normal ventilation and drainage in the lung. Bronchoscopic aid is principally through the removal of obstruction. Obstruction may be due,

- 1 To foreign body, aspirated or endogenous,
- 2 To stenosis or deformity of the bronchi,
- 3 To tissue obstruction from inflammatory or neoplastic change,
- 4 To secretion, normal or abnormal

Foreign Body Bronchoscopic removal of foreign body, with 98 per cent cure is generally accepted as the only worthwhile method of treatment. This applies either to aspirated or to endogenous foreign bodies. Bronchoscopic removal is accomplished by the use of forceps through the bronchoscope and by those trained in bronchoscopic procedure is accomplished without general anesthesia. In cases where the foreign body has passed beyond the point where it can be seen through the bronchoscope,

biplane fluoroscopic guidance may be used. If the bronchoscopist and roentgenologist have mastered a cooperative technique, the procedure is usually without serious risk. In cases of foreign body where the density of the object is such that it can be localized only on the roentgen-ray film and not fluoroscopically, the technique of Pancoast and Pendergrass can be used and opaque markers placed in such a position that roentgenoscopic localization may be made and bronchoscopic removal successfully carried out under fluoroscopic guidance.² (See Case 2.)

Bronchial Stenosis It is evident that the character of the lesion producing the stenosis will determine the desirability of bronchoscopic dilatation. A simple cicatricial stenosis of the bronchus may be dilated readily by direct vision by use of the bronchoscope. A compression stenosis may also be dilated bronchoscopically. The nature of the compression should, however, be known and its character should determine the method of treatment.

Stenosis due to inflammatory tissue is frequently amenable to bronchoscopic treatment. Benign endobronchial neoplasms may be removed bronchoscopically. Malignant tissue may be removed, and radon may be implanted in obstructing tissue, with removal of obstruction and relief of the secondary infective processes that so frequently are due to obstruction of the bronchus by malignant neoplastic tissue. In cases of cancer of the lung with bronchial stenosis, the results of irradiation treatment can best be determined by bronchoscopic examination.

Bronchoscopic Removal of Secretions The bronchoscopic aspiration and removal of secretions that obstruct the airway is probably the most important contribution of the bronchoscope, aside from foreign body removal. In certain conditions where the cough mechanism has been temporarily impaired, postoperatively or post-partum, acute edema of the lungs and acute obstruction by retained secretion result, as in massive collapse of the lungs. The patient is unable to free the tracheobronchial tree from obstruction. The same conditions sometimes occur in asthma.³ In this type of case the mechanical removal of obstructing secretion through the bronchoscope prevents asphyxial death and produces a cure that seems little short of miraculous. In inflammatory lesions, particularly in post-operative pulmonary complications, bronchoscopic removal of obstruction prevents the more serious lesions such as lung abscess, etc. In subacute and chronic pulmonary infections bronchoscopy may prevent bronchiectasis. This is particularly true of unresolved pneumonia, purulent tracheobronchitis, purulent tracheobronchitis with drowned lung and drowned lung where the secretions are retained after the removal of foreign body. The bronchoscopic removal of secretions from the bronchi aids ventilation and drainage and allows the inflammatory processes to resolve. Repeated bronchoscopic aspiration has, in many patients, completely restored the lung to normal.

Bronchoscopic aspiration removes the secretion in two ways. First by direct aspiration through the bronchoscope or aspirating tube. With

a flexible-tipped aspirating tube, bronchi that diverge at an angle from the main bronchi may be aspirated. The curved flexible tip permits aspiration around the corner. Second, bronchoscopic treatment brings about removal of secretion by the production of "selective cough."

"Selective Cough" as a Means of Pulmonary Drainage On the introduction of the bronchoscope or aspirating tube into the uncocainized area of lung, there occurs a deep inspiratory effort with an extreme widening of the bronchial orifices and a violent expiratory effort which frequently can be seen to force casts of the smaller bronchi and plug-like masses of purulent secretion into the lumen of the larger bronchi in front of the bronchoscope. The removal of the obstructing material from the smaller bronchi allows free drainage of the area of lung beyond, and as a result, we find that the patient frequently continues for several days to bring up large quantities of secretion. During this time there will be evidence on physical examination that the lung is clearing. This is one of the most important results of bronchoscopic aspiration.

Bronchoscopic Medication and Disinfection in Pulmonary Disease The introduction of medication bronchoscopically does not have a satisfactory status at the present time. It certainly is undesirable to instil oils into the lung as medication, or to flood the lung with anything in the nature of an antiseptic solution. The introduction into the larger bronchi of a mild antiseptic solution such as 1 to 10,000 mercuraphen, followed by bronchoscopic aspiration, may be desirable, not so much because of the disinfecting power of the solution as that it acts as a diluent and permits the removal of tenacious secretion, thereby allowing free drainage. At the suggestion of the author and Dr. Chevalier Jackson, Dr. John A. Kolmer carried out a very interesting series of experiments in animals in bronchial disinfection and immunization.⁴ However, the practical results of this experimentation have not as yet been fully determined. It would seem when substances, either chemical, bacteriological or serological, are produced, suitable for use in the lung for sterilization and disinfection that the best method of application will be through the bronchoscope because the medication can be controlled and restricted to the diseased lobe of the lung. When a considerable quantity of fluid material is introduced into the lung, it should be reaspirated promptly. If it is not aspirated, one should, from the local condition of the lung, be reasonably certain that it would be removed promptly by cough. In the use of iodized oil for pneumonography particular care is used not to force the opaque material into the lung but to allow gravity and the respiratory efforts to carry it in.

As an adjunct to free drainage, all medication that will tend to prohibit the normal cough mechanism should be withheld, particularly opiates and other cough sedatives. The use of atropine is also undesirable because it increases the viscosity of pulmonary secretions and makes it more difficult to expel them from the lung by the cough mechanism.

Dr William F Moore, at the Philadelphia General Hospital, has obtained very favorable results from the bronchoscopic intrabronchial application of polyvalent bacteriophage prepared from stock culture⁵ This type of bacteriophage seems at the present to give us the most hope for benefit in the field of intrabronchial medication The best method of application is by means of the bronchoscope, because the field of application can be limited, its action noted by inspection, and the procedure better controlled

Contraindications to Bronchoscopy There are few contraindications to bronchoscopy where there is a positive indication for its use In every case in which it is possible a careful roentgen-ray examination and a physical examination by a competent internist should be made, prior to bronchoscopic examination

Modification of Bronchoscopic Technic In patients urgently dyspneic where there is evidence of bronchial obstruction, as in postoperative pulmonary complications, bilateral atelectasis, acute edema of the lungs such as is seen occasionally post-partum in heart lesions, bronchoscopy may be done for the removal of obstructive secretions without removing the patient from the bed⁶ In a number of instances in a grave emergency of this type, bronchial obstruction has been relieved by bronchoscopic aspiration of secretions The limit of the use of bronchoscopy where it is indicated, then, must be a matter of the efficiency of the bronchoscopic technic

Illustrative cases of the results of bronchoscopic aid in the diagnosis and treatment of conditions which occur frequently in the ordinary run of patients seen by the internist are here presented

Chronic Cough Chronic unexplained cough in a patient who has been studied carefully by the usual diagnostic method is frequently encountered A simple bronchoscopic inspection of the tracheobronchial tree will reveal the cause in many cases and afford a means of treatment that will cure the condition

CASE I

Chronic cough, bronchial obstruction, localized bronchial dilatation

A male, 45 years of age, an attorney referred by Dr William MacMurtrie of Philadelphia, had chronic intermittent coughing attacks, more severe at night, over a period of years The patient was well nourished and not otherwise ill The strangling cough became so severe that he was unable to follow his occupation The condition had been variously diagnosed as chronic bronchitis, asthma, etc Finally the patient's condition became progressively worse and a careful roentgen-ray check-up and physical examination revealed an abnormal density and area of dullness in the posterior portion of the right lower lobe Bronchoscopic examination revealed a tumor mass blocking the posterior division of the right lower lobe bronchus The obstructing tissue was removed bronchoscopically and found to be inflammatory tissue, and a localized area of bronchiectasis secondary to the obstruction of the bronchus was demonstrated by lipiodol (Figure 1) After removal of the tumor bronchial drainage was restored, the dilated bronchi returned to normal and the patient's symptoms entirely disappeared The patient has been well three years

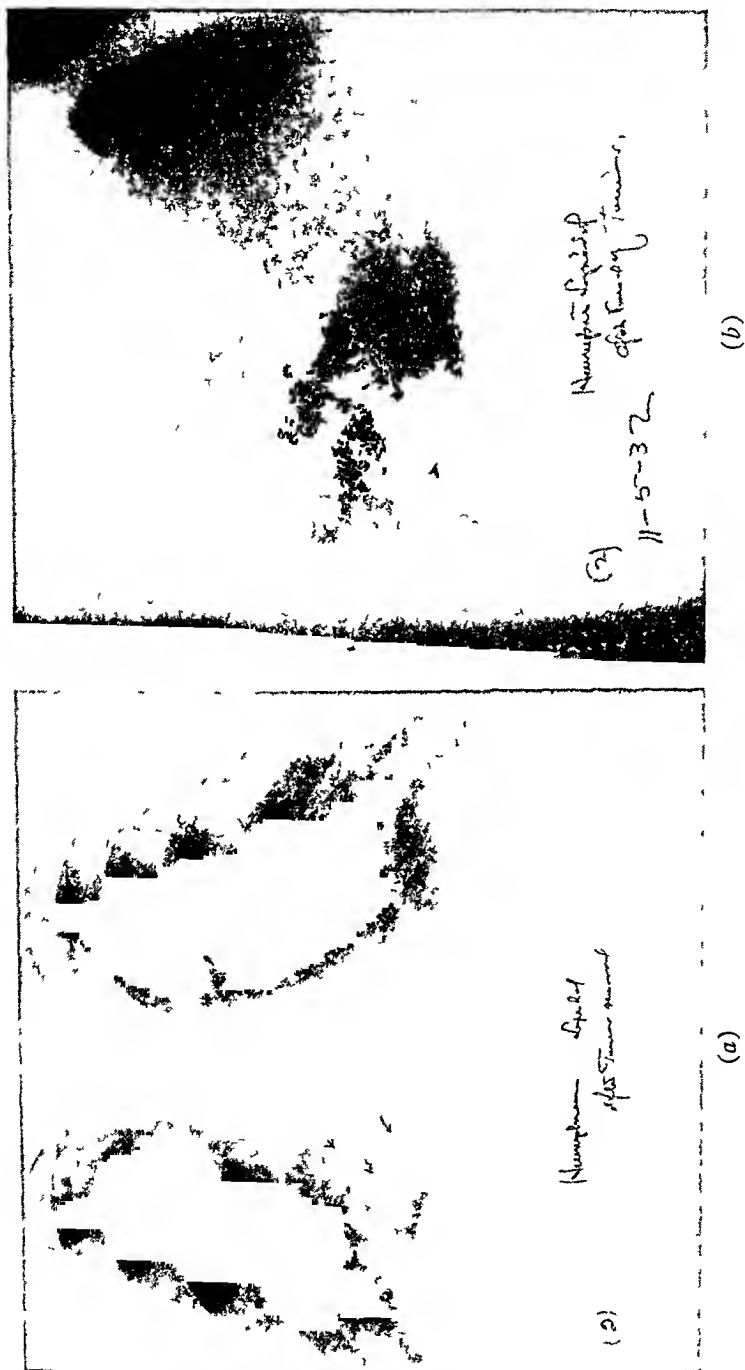


FIG 1 Case 1

Bronchoscopic lipiodol pneumonogram showing the area of bronchial dilatation distal to the location of tumor
 (a) Anteroposterior
 (b) Lateral

The lipiodol was coughed out. The lung cleared completely after six bronchoscope treatments.

Hemoptysis Active pulmonary hemorrhage is practically always a contraindication to bronchoscopic examination. Where the condition is not definitely due to tuberculous infection, bronchoscopic examination in the interval between periods of hemoptysis will frequently establish a diagnosis. Overlooked foreign body, carcinoma of the lung, benign tumor of the lung, inflammatory granulation in a bronchiectatic cavity, ulcerative lesion of the bronchus, broncholithiasis, granuloma of the bronchus, pulmonary tuberculosis in which acid-fast organisms had not been demonstrated from sputum examination, each has been established definitely, by bronchoscopic examination, as the cause of hemoptysis.

CASE II

Hemoptysis, overlooked foreign body

A male, 29 years of age, had had a slight hemorrhage five weeks before admission, a week later a severe hemorrhage, a week following this a third hemorrhage, and three days later a fourth. After several roentgen-ray examinations were made a small dense shadow was detected in the lower lobe of the right lung, near the right border of the heart. In going back over the history it was found that the patient had had extraction of teeth under general anesthesia 15 years and nine years before admission. Following the second tooth extraction there had been a dry cough. The patient's general condition had been otherwise good. The diagnosis of foreign body in the lung was made by Dr. Channing Frothingham of Boston who referred the patient. A special roentgen-ray examination showed that the dense shadow was probably a fragment of a tooth. Bronchoscopy for removal of the foreign body was done under fluoroscopic guidance at the University of Pennsylvania Hospital, after roentgen-ray localization of the tooth by Dr. Pancoast and Dr. Pendergrass, and the foreign body removed (Figure 2 *a, b, c*). In order to obtain fluoroscopic guidance it was necessary to use a special method of localization. Opaque markers were placed anteroposteriorly and laterally with the patient in the recumbent position after the method of Dr. Pancoast and Dr. Pendergrass, because the tooth was not dense enough to be seen fluoroscopically although it could be demonstrated very well on a *Bucky* film. This case illustrates overlooked foreign body as a cause of pulmonary hemorrhage, and also demonstrates the effectiveness of properly guided fluoroscopic bronchoscopic removal of a foreign body that was not sufficiently opaque to be seen on fluoroscopy.

Bronchial Tumors, Benign and Malignant The diagnosis of bronchial tumor is made certain in a great majority of cases by bronchoscopic examination. Biopsy is possible in many tumors both benign and malignant. Benign tumors may be removed endoscopically while malignant tumors may be treated by radon implantation through the bronchoscope. The secondary pathology, drowned lung, abscess, etc. may be benefited during the irradiation treatment by repeated bronchoscopic aspiration of secretions from the obstructed area of lung. This is especially emphasized by Dr. Eugene Pendergrass who insists on bronchoscopic drainage during the irradiation treatment of his cases of pulmonary tumor. Tumors of the mediastinum and the lung itself may also be diagnosed by bronchoscopy in a percentage of cases.⁶ Occasionally a pulmonary tumor may give esopha-

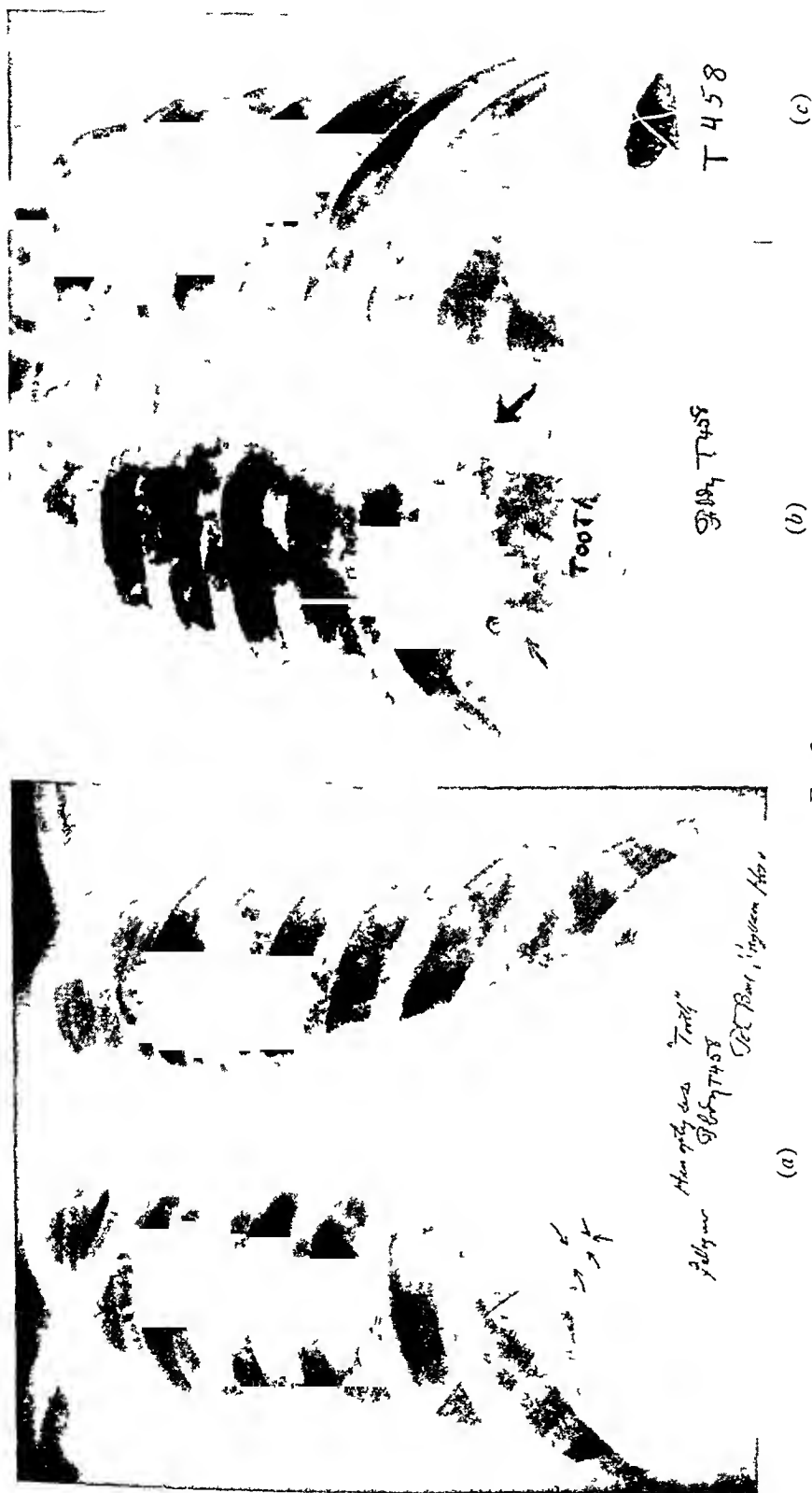


FIG 2

- (a) Roentgenogram showing tooth shadow at the junction of the diaphragm and heart shadow. Tooth shadow could not be seen fluoroscopically.
- (b) Roentgenogram showing opaque marker in position. Pencoast-Pendergrass technic. Markers could be seen fluoroscopically and were so placed that they served as guides for the location of the tooth during bronchoscopic removal. The bronchoscopist used the sense of touch as a guide in grasping and withdrawing the tooth.
- (c) Fragment of tooth after removal.

geal symptoms, due to periesophageal extension, and the differential diagnosis can be made only by bronchoscopic examination (Figure 3)

CASE III

Primary carcinoma of the lung, metastatic extension producing compression stenosis of the esophagus

Male, aged 58 years The patient was referred because of dysphagia and loss of weight by Dr J S McKee of Norfolk, Virginia He was emaciated and able to swallow only liquids He complained of cough only when lying down Roentgen-

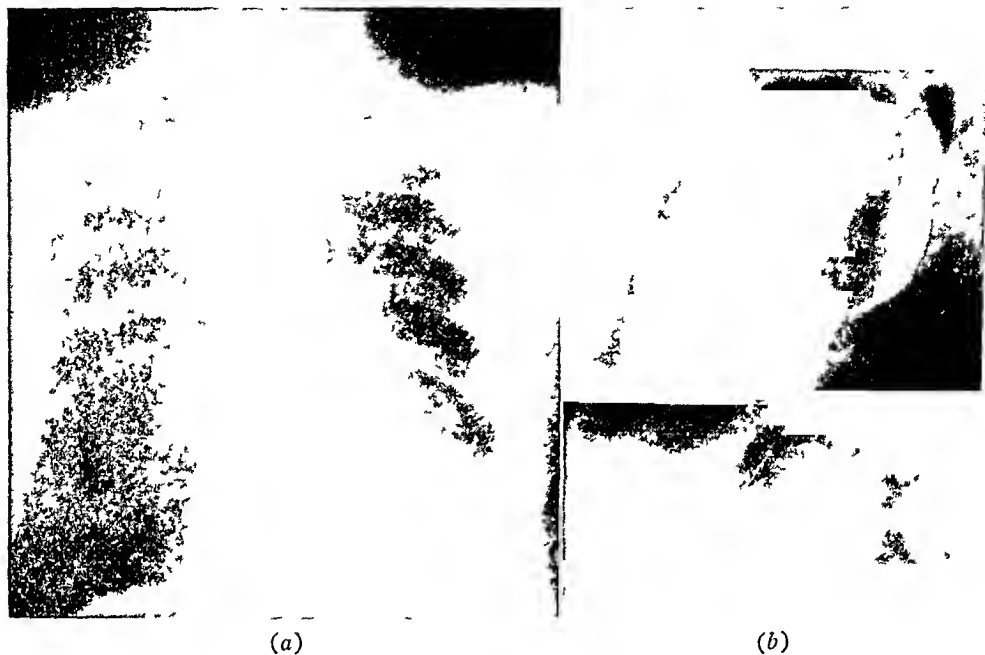


FIG 3

(a) Roentgenogram showing evidence of peribronchial thickening at the left base On bronchoscopy, tissue removed from left lower lobe bronchus showed carcinoma

(b) Lateral film, with opaque mixture, shows stenosis of the lower esophagus Esophagoscopy showed compression, no ulceration The triangular area in front of the shadow of the lower esophagus represents atelectasis due to bronchial occlusion by the cancer in the left lower lobe

ray examination showed a stenosis of the esophagus involving the lower third, evidence of an old tuberculous lesion in the apices of both lungs, and increase in density at the left base, the suggestion being that this might be due to a bronchiectasis The esophagoscopy examination revealed an annular stenosis involving the lower third of the esophagus, and on passing a small esophagoscope in the strictured area the mucous membrane was found to be smooth, the lesion apparently being periesophageal with no ulceration

Because of the roentgen-ray evidence of a lesion in the left lower lobe, bronchoscopic examination was made which showed an organic stenosis of the left lower lobe bronchus with firm infiltration and ulceration of the bronchial wall Histologic diagnosis by Dr E A Case was "bronchial carcinoma," from bronchoscopic biopsy The bronchoscopic finding in this case enabled us to make a diagnosis of primary

carcinoma of the bronchus with periesophageal extension producing compression stenosis of the esophagus. These findings were confirmed later in this patient by autopsy.

Tuberculosis In the ordinary case of uncomplicated pulmonary tuberculosis with a positive sputum there is no indication for bronchoscopy. In suspected cases where the sputum is negative, bronchoscopically removed secretion from the involved area of lung frequently shows tubercle bacilli and confirms the diagnosis. The presence of a tuberculous infection is not a contraindication to bronchoscopic examination. A persistent wheeze, obstructive emphysema, obstructive atelectasis or drowned lung are indications for bronchoscopy.

CASE IV

Pulmonary tuberculosis, bronchial stenosis

Female, aged 40, referred by Dr Frank Burge of Philadelphia because of a persistent expiratory wheeze and evidence of emphysema of the left lung. Dr Burge had made a diagnosis of tuberculosis in this patient, had placed her in a sanatorium and, with pneumothorax treatment, had arrested the disease. The patient had gained weight to above normal, and the sputum was free of tubercle bacilli. Physical ex-

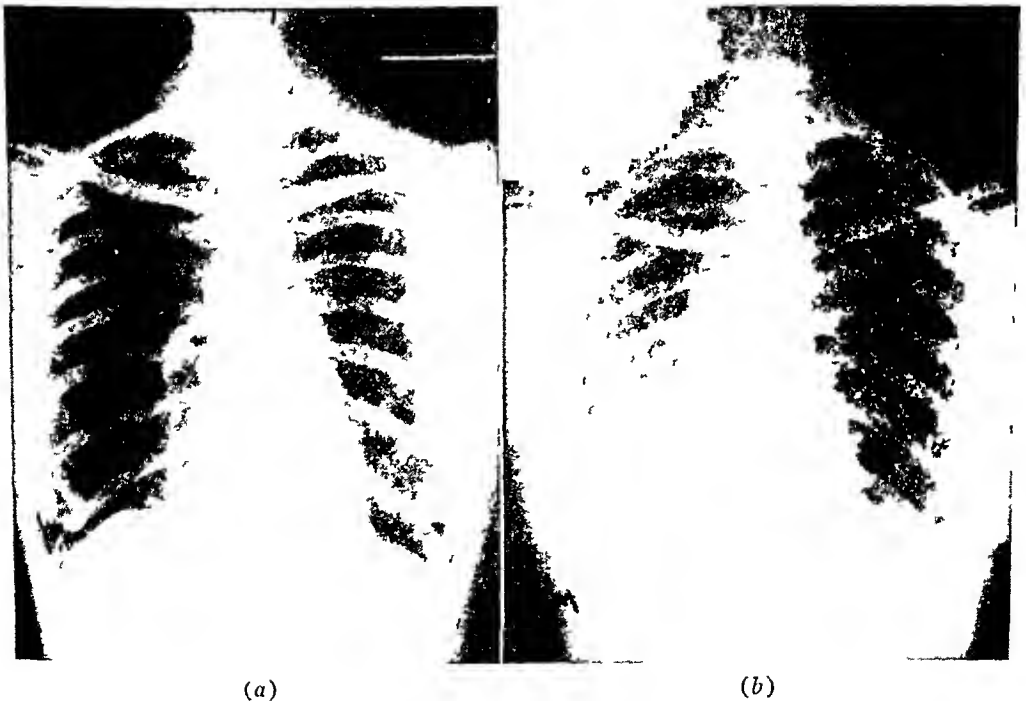


FIG 4 Case 4

(a) Anteroposterior chest film, taken on inspiration, showing the heart in normal position.

(b) Anteroposterior film on expiration showing displacement of the heart to the right, marked depression of the left diaphragm, the characteristic findings of obstructive emphysema.

Bronchoscopic examination showed the obstruction to be due to tuberculous granulation tissue obstructing the left main bronchus.

amination gave evidence of bronchial stenosis and roentgen-ray examination showed marked obstructive emphysema of the left lung. Bronchoscopic examination revealed fungating masses of tissue in left main bronchus which obstructed the airway to such an extent that the left bronchus was almost completely blocked on expiration. The tissue masses were removed bronchoscopically and the tissue, examined by Dr E. A. Case, was reported as showing "chronic exudate and tissue the seat of tuberculosis".

Removal of the masses relieved the bronchial obstruction to a considerable extent and so far there is no evidence of recurrence of this type of tissue. There is, however, evidence of stenosis of the left main bronchus which has been relieved by bronchoscopic dilatation. A full report of this case will be made subsequently by Dr. Burge.

Suppurative Disease of the Lung In every patient with suppurative lesion of the lung, unless it is one in which there is pleural involvement with urgent demand for external surgery, bronchoscopic investigation as an aid to diagnosis and localization of the lesion should be carried out.

Bronchiectasis Bronchoscopic examination will reveal the condition of the interior of the larger bronchi. Aspiration of secretion and bronchoscopic pneumonography will best demonstrate the extent of the lesion. If bronchial obstruction can be relieved by intrabronchial treatment the function of the diseased area of lung may be restored. If no improvement results the information obtained by the study will be of aid to the surgeon in classifying the condition for surgical treatment, that is, it will help to decide whether the patient has a "first, second or third degree bronchiectasis".⁸ In advanced bronchiectasis, bronchoscopy is palliative only, and if surgery is not done, bronchoscopic treatment combined with postural drainage and medical care will make the patient's burden easier. Every case of bronchiectasis should have careful bronchoscopic study before the diseased area of lung is excised.

Prevention of Bronchiectasis by Bronchoscopy There is much controversy regarding the exact etiology of bronchiectasis. There is, however, a factor which has been emphasized little except by Chevalier Jackson, namely, localized infection of the lung, with obstruction to the normal bronchial drainage. There are a number of pathological conditions which are undoubtedly followed by bronchiectasis in which, if normal drainage is restored and maintained by way of the tracheobronchial tree, bronchiectasis will be prevented. Of these conditions may be mentioned unresolved pneumonia, purulent tracheobronchitis, localized infection with obstruction and drowned lung, pulmonary changes following the sojourn of foreign body.

CASE V

Unresolved pneumonia

Female, colored, aged 25, referred from the service of Dr. George M. Piersol, Graduate Hospital, University of Pennsylvania. This patient had developed an extensive lesion in the right chest which had been under observation for a period of six weeks. The course of the disease was at first typical of pneumonia, her temperature then became septic, and the lesion extended until it involved the entire right lung. Her general condition remained about the same (Figure 5). The lung

failed to clear and she was referred for bronchoscopic examination. Following the first bronchoscopy there was very profuse expectoration of foul pus. A second bronchoscopy was done three days later. Her temperature then remained normal, the quantity of pus expectorated gradually lessened. Four bronchoscopic treatments in all were given. Her condition improved to such an extent that she was dis-

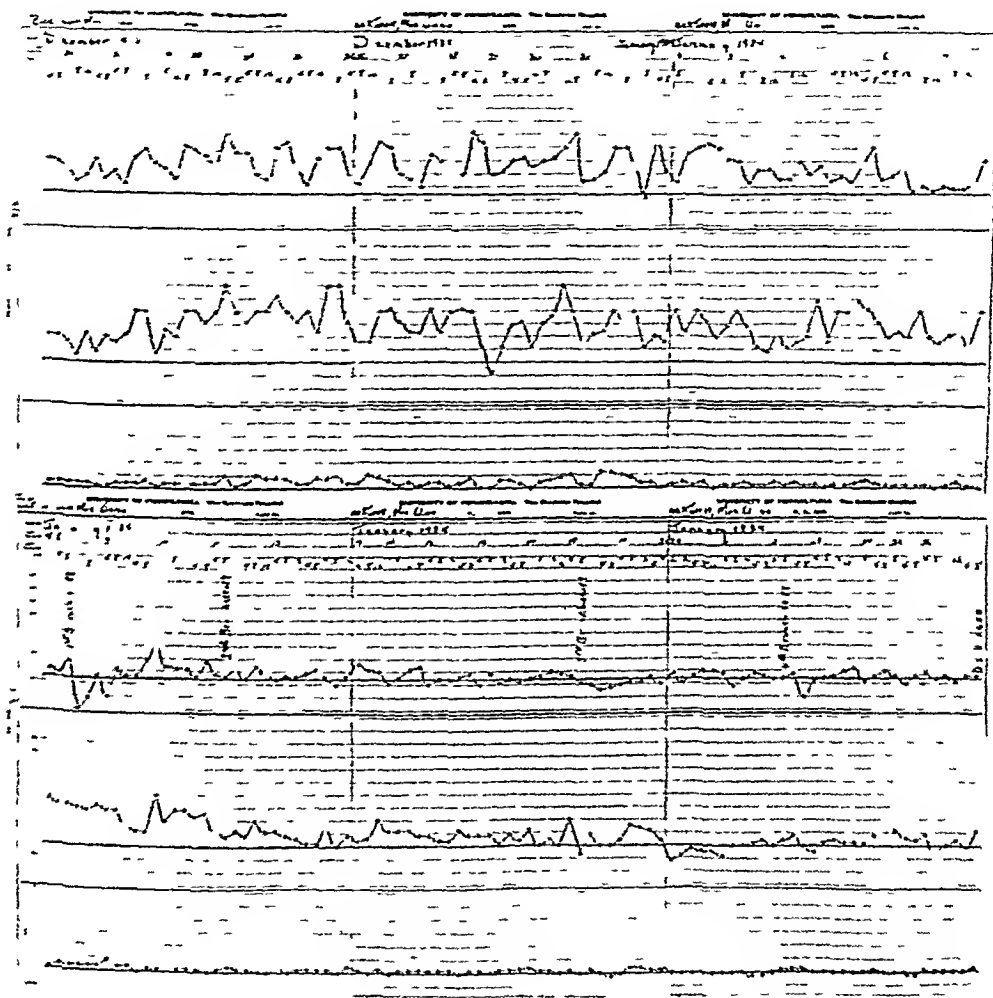


FIG 5 Clinical chart showing the course before, during and following bronchoscopic treatment

charged from the hospital after two weeks treatment. She has been kept under observation as an out-patient for a period of six months and her lung is entirely clear (Figure 6)

Postoperative Pulmonary Complications Postoperative pulmonary complications, in many cases, require bronchoscopic examination as a means of differential diagnosis to exclude aspiration infection or foreign body. Bronchoscopy should be done early as a diagnostic examination and it will

very frequently promote drainage to such an extent that prompt resolution of the condition will occur

In massive collapse where other measures do not promptly restore the lungs to normal, bronchoscopic aspiration will open the airway and restore ventilation and drainage. One of the most important factors in the production of postoperative pulmonary atelectasis is impairment of the cough

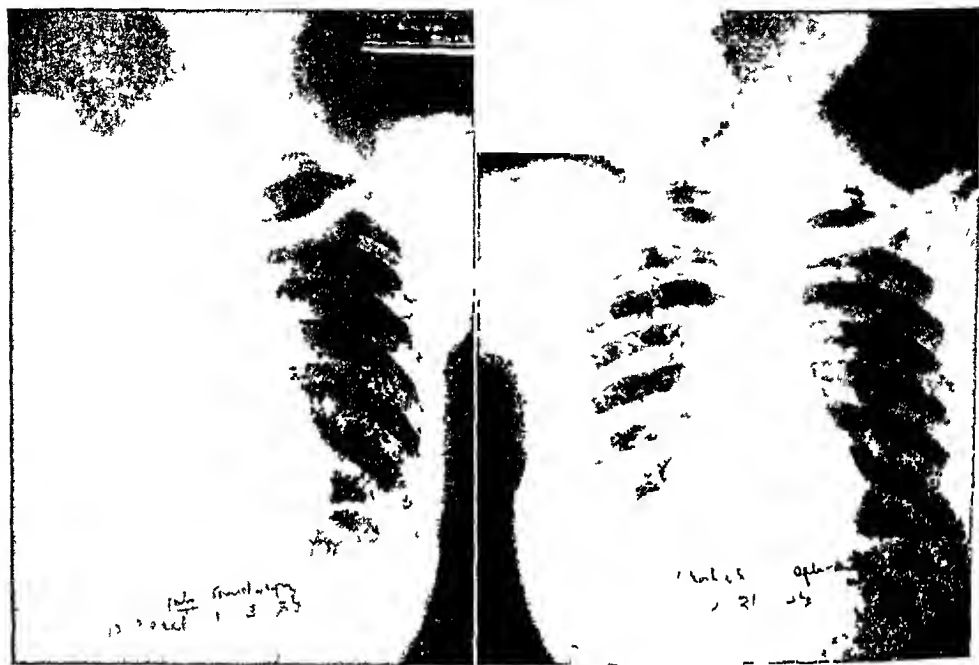


FIG 6 Roentgenogram showing the chest condition before bronchoscopic examination and after bronchoscopic cure

mechanism as the result of operative procedure. In these cases bronchoscopy may be required to supplement the coughing efforts in the removal of obstructive secretions.⁷

CASE VI

Postpartum edema of the lungs

A woman, 35 years of age, was referred by Dr Arthur First of Philadelphia. She had been delivered of a normal child at term without instrumentation. The patient had a mitral stenosis, well compensated. Within 24 hours she developed an acute edema of the lungs although her heart condition was pronounced by Dr Henry Smookler to be satisfactory. When seen in consultation she was propped up on a back rest. The tracheobronchial tree was rapidly filling with secretion which she was unable to remove by coughing efforts. The medical consultant assured us that her heart condition warranted bronchoscopic aspiration. A modified bronchoscopic technic was used without removal of the patient from bed. About 150 cc of thin brownish secretion were aspirated from the tracheobronchial tree. Dyspnea was immediately relieved, there was no recurrence of the pulmonary edema, and the patient progressed to an uneventful recovery (Figure 7)

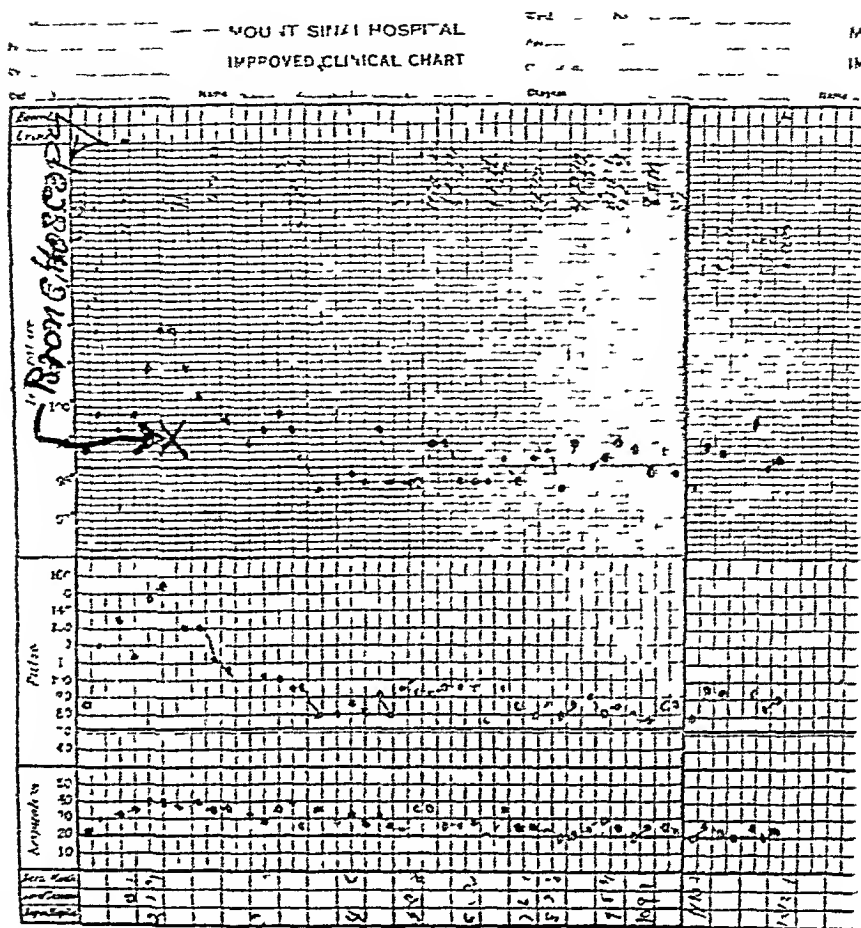


FIG 7 Clinical chart showing patient's condition at and subsequent to bronchoscopic removal of obstruction.

CONCLUSIONS

1 Due to the perfection of instrumentarium and of the method of bronchoscopic procedure without general anesthesia, bronchoscopy has reached a point in development where it is invaluable as an aid in the diagnosis and treatment of pulmonary disease

2 The bronchoscopic findings will supplement all other methods of examination in pulmonary disease. In order to obtain the best results, special training and continuous practice by the bronchoscopist is required, together with a trained personnel, adequate instrumentarium and the support and close cooperation of the internist, the roentgenologist and the surgeon.

3 Modern bronchoscopy has developed a world-wide interest because of its efficiency as an aid in the diagnosis and treatment of pulmonary disease. Its continued advance and development will depend upon the interest and support given by the internist and the pediatrician who see the patients first and who decide whether or not the patients shall have the benefit of bronchoscopic consultation.

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THE IMPORTANCE OF ACTUALLY MEASURING THE TOTAL HEAT PRODUCTION

By L. H. NEWBURGH, *Ann Arbor, Michigan*

A KNOWLEDGE of the basal metabolism is informative in many different problems. Its diagnostic value is quite familiar, but its use as a basis for estimating the total production of heat is open to errors which are sometimes so large that the observer is seriously misled.

In the pursuit of our own studies, it became of paramount importance to be possessed of a means of knowing accurately how much energy was dissipated day after day so that we could compare the inflow of calories with their expenditure. This we were able to do by the development of Benedict's¹ study of the insensible perspiration. Time does not permit a discussion of the method. It is described in detail in our publications². Suffice it to say here that it is capable of yielding extremely accurate data when the proper precautions are followed.

The earlier way of estimating the total heat production consisted of adding to the basal metabolism, theoretical increments appropriate for the activity of the subject.

In 1918, as a war measure, Lusk³ made such prediction tables. The average weight of thousands of individuals of a given height at 35 years of age, was calculated. The normal basal metabolism was then figured by means of the DuBois height-weight formula. To these basal values, 10 per cent for 16 hours was added to provide for sitting and standing. Tables for the extra calories per hour attributable to various occupations were then consulted and the values for an eight hour day corresponding to the occupation were added to the sum already obtained. A final increment of 200 calories for men and 150 calories for women was included to account for small movements such as dressing. Part of the information may be seen in table 1. The theoretical basal metabolism was 1700 calories for 24 hours.

TABLE I

| Predicted Increment Corresponding to Activity Per cent of Basal | Total | Type of Activity |
|--|-------|------------------|
| 6 | 1800 | Bed |
| 40 | 2375 | Tailor |
| 60 | 2730 | Shoemaker |
| 94 | 3300 | Carpenter |
| 160 | 4400 | Stone Mason |
| 196 | 5025 | Woodsmen |

* Read at the Chicago meeting of the American College of Physicians, April 17, 1934

It must be remembered that these predictions were theoretical and that no test of their accuracy was made. The first three values are strikingly low. It is especially difficult to accept the statement that the patient in bed expends only 100 calories beyond the basal. Most writers have assumed that 20 to 30 per cent needed to be added to the basal metabolism to arrive at the total expenditure of energy for persons in bed. It requires only a moment's thought, however, to make one realize that the variations from patient to patient must be large. It seems unlikely that any general prediction for this group of persons can have much value.

We have applied our method for measuring total heat production to three youths who had been in bed for some months because of minimal tuberculosis of the lungs. All were afebrile and entirely free of symptoms. It might be supposed that their long experience in bed had taught them to be reposeful. The facts revealed by actual measurement came as a great surprise to us.

TABLE II
Basal and Total Production of Heat by Boys Continuously in Bed

| Patient | Basal Metabolism Cal for 24 Hours | Total Metabolism | |
|------------|--------------------------------------|------------------|-----------------------------------|
| | | Cal for 24 Hours | Increment in per cent of basal |
| E P age 18 | 1550 | 2558 | 65 |
| C S age 15 | 1550 | 2325 | 50 |
| H J age 18 | 1580 | 2350 | 49 |

Nor were the total calories increased when these patients were permitted the freedom of the room.

We had a similar experience with a normal subject who was first in bed for a week and was then allowed to move freely about the room during the second week. These experiences give rise to the question whether anything is gained by forcing patients to remain continuously in bed when they do not feel ill enough to stay there voluntarily. Perhaps they would often expend less energy if they were permitted to make themselves comfortable within the confines of a large and pleasant room.

We have also recorded the heat production of a series of men and women while they were pursuing their usual modes of life. Table 3 contains the data. The increment of expenditure of energy varies from 53 to 120 per cent. Leaving out the last subject, it is noteworthy that a group of young people, none of whom was earning his livelihood by manual labor, expended an amount of energy roughly equal to their basal metabolism as a result of the day's activities. Examination of the individual values should convince the reader that a prediction of the total heat production for any one of the subjects would be liable to a large error.

We have determined the total dissipation of energy by obese persons and compared these values with the calories of the diet. We have then predicted

TABLE III
Total Energy Metabolism for Various Activities

| Sex | Age | Wt Kg | Ht Cm | Basal Me- tabolism Cal for 24 Hours | Total Metabolism | | Occupation |
|-----|-----|----------|----------|--|---------------------|---|------------------------------------|
| | | | | | Cal for 24 Hours | Increment in per cent of basal | |
| M | 24 | 61 | 180 | 1490 | 2586 | 73 | Student of architecture |
| F | 35 | 53 | 154 | 1150 | 2075 | 80 | Nurse in charge of clinic |
| M | 30 | 56 | 174 | 1561 | 2975 | 90 | Intern |
| M | 28 | 57 | 183 | 1452 | 2920 | 101 | Laboratory worker |
| F | 24 | 73 | 168 | 1633 | 3210 | 96 | Laboratory worker |
| M | 25 | 67 | 175 | 1691 | 3425 | 102 | Medical student |
| M | 23 | 64 | 165 | 1623 | 3570 | 120 | Graduate student in chem- istry |
| M | 24 | 66 | 174 | 1685 | 3550 | 111 | Graduate student in chem- istry |
| M | 56 | 70 | 180 | 1630 | 2500 | 53 | Retired, sedentary habits |

the loss of weight and in that way we have convinced ourselves that all obese persons will lose weight when they are underfed, and what is more important, that these individuals have invariably become fat simply and solely because they have eaten too much

We have recently had the opportunity of studying a patient of the type described by Cushing. The outstanding characteristics are uniform decalcification of the skeleton and adiposity of the upper half of the body. Figure 1 shows the patient, 19 years old, who is only 5 feet tall, when he weighed 180 pounds. You will note that his legs and arms are not at all fat but that he appears to possess a huge deposit of adipose tissue in the chest and abdomen. This apparent localization of the fat lends an air of mystery to the situation and is generally interpreted as evidence that the gain in weight is not merely due to overeating. The baneful intervention of an endocrine gland is suspected. After this patient had lost 50 pounds in response to a diet of about 900 calories, photographs were made again (figure 2). This time the weight of 132 pounds is normal and still the chest and abdomen are as protuberant as they were in the beginning. Examinations by the roentgen-ray (figure 3) show that the spine is unusually short and hence much less than the normal space was provided for the organs. The necessary room has been obtained by an upward and outward movement of the ribs. What superficially appears to be a localized accumulation of adipose tissue is in fact merely the configuration of a deformed skeleton. As further evidence that there is nothing peculiar about the obesity of this patient, attention is called to figure 4. The solid line represents the actual loss of weight in response to underfeeding. The broken line indicates the predicted decline in weight calculated from the difference between the total expenditure of energy and the calories of the diet. It is difficult

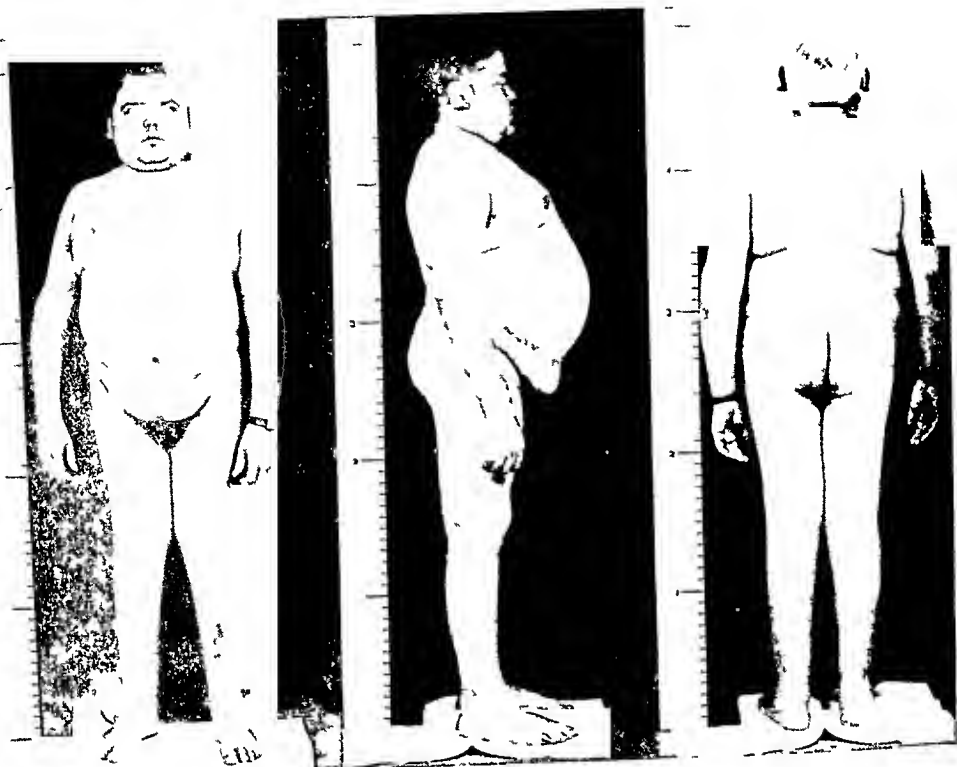


FIG 1

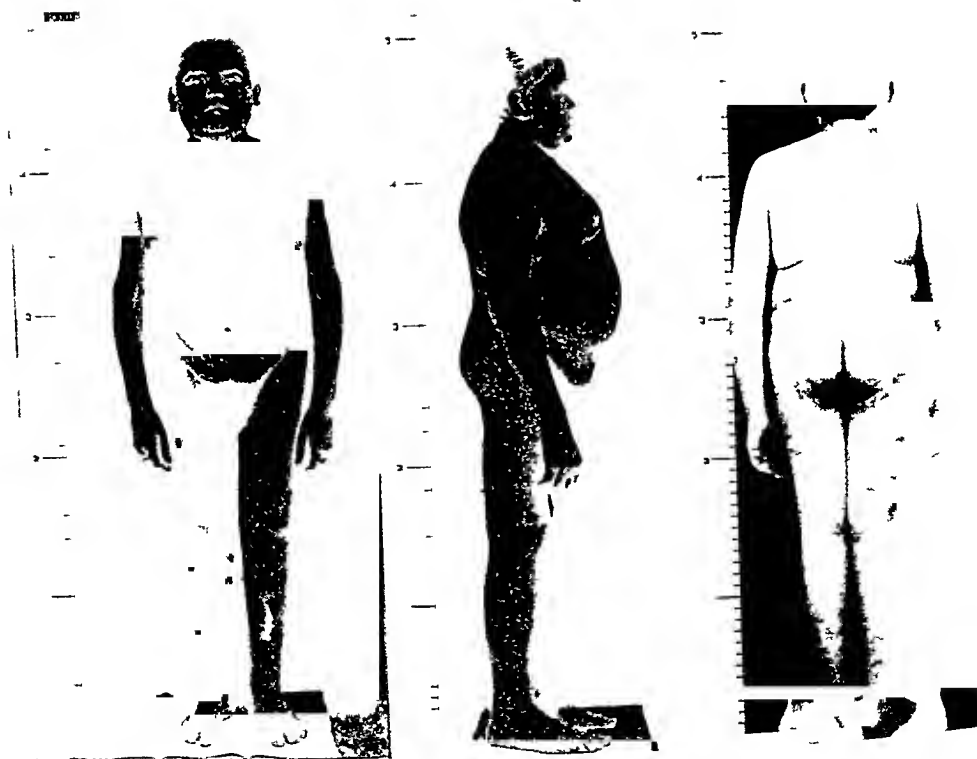


FIG 2



FIG 3

to believe that an individual, whose weight during a period of 54 days was reduced by underfeeding to within 22 grams of the predicted value, could have become fat for any reason other than overeating

The next patient is interesting because of the dramatic response to undernutrition. He exhibited enormous localizations of adipose tissue and his initial weight of 560 pounds was astoundingly great. Both features are often credited with being signs of endogenous obesity. His appearance at the beginning of treatment is shown in figure 5. During the ensuing year his diet afforded him 300 calories a day. This effected a loss of weight of 287 pounds (figure 6). During the second year he received 600 calories daily and lost 93 more pounds. He now weighed 194 pounds, a weight that was considered satisfactory for his height. He was now told to keep his weight stationary by judicious selection of his food. How well he succeeded is shown in figure 7, taken nine months after he had been told that he had lost a sufficient amount of weight, since he weighed the same amount.

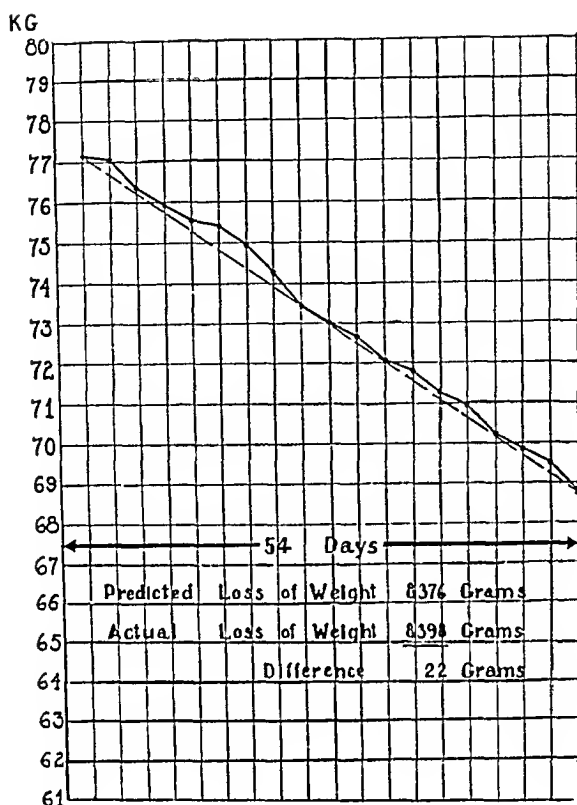


FIG 4

Grafe,⁴ in his book published within the year, states that obese individuals who maintain their weight for a period of time in spite of underfeeding, are victims of endogenous obesity. If this were true, the responses portrayed in figure 8 could not have occurred. This adipose female who was in bed throughout the study expended close to 2500 calories daily. When her diet contained that number of calories, she neither gained nor lost weight (first period). She next received about 1800 calories from a diet high in carbohydrate—260 grams daily. She responded by a steady loss of weight (solid line) that corresponded with the predicted loss (broken line). In the final period she also received about 1800 calories but now the diet contained little carbohydrate and much fat. This caused an initial precipitous loss followed by a period during which she did not lose weight. Since both types of response were produced in the same individual by manipulation of the diet, I think you will agree that the manner in which the weight responds to dietary treatment is not determined by something within the individual but rather by the character of the diet.

Furthermore, this ability to maintain the weight in the face of underfeeding is not the sole possession of obese persons since we have reproduced



FIG 5

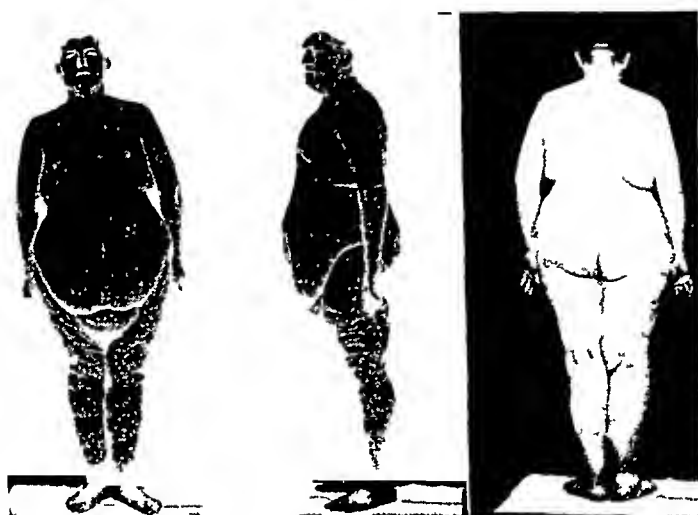


FIG 6

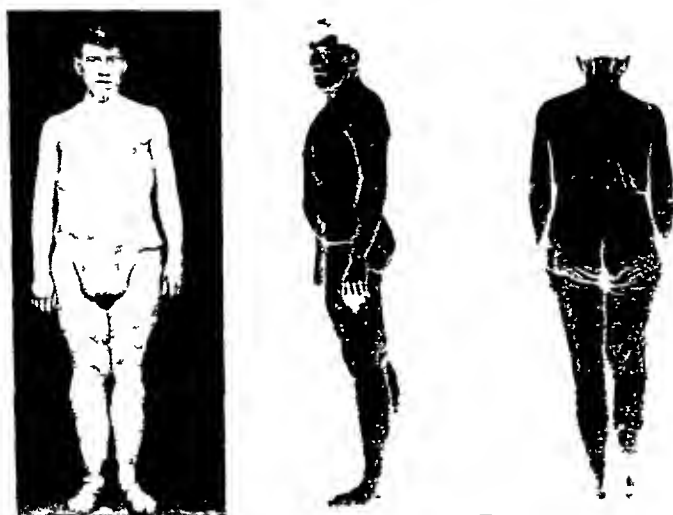


FIG 7

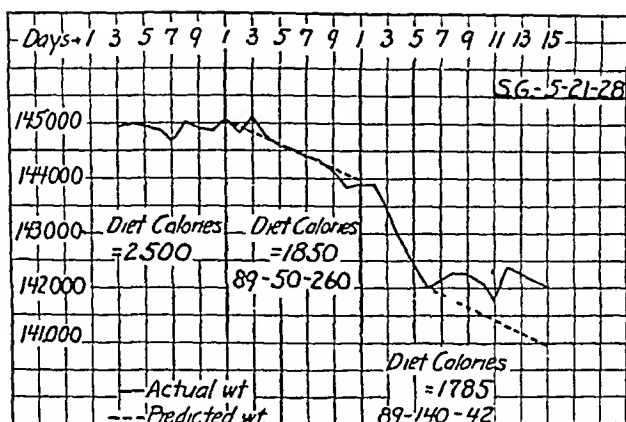


FIG 8

it in the normal as may be seen in figure 9. This normal man who was in bed throughout the study, received 1078 calories daily in the form of 69 grams of protein, 91 grams of fat and 148 grams of carbohydrate. He

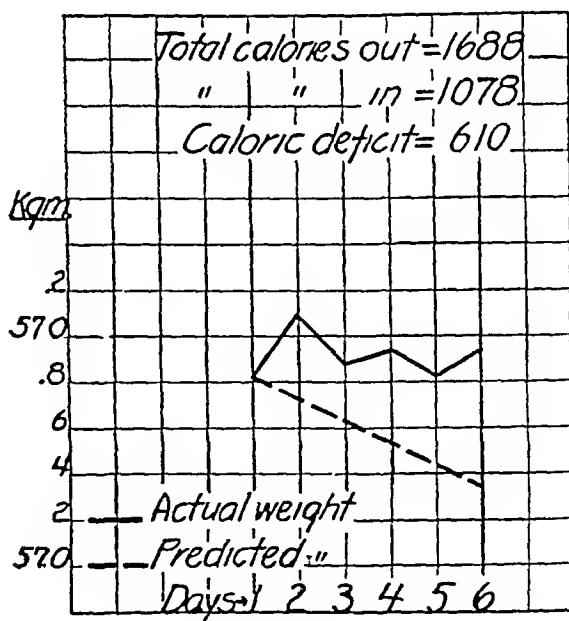


FIG 9

dissipated 1688 calories a day. The diagram shows a period of five days during which he destroyed 475 grams of bodily tissue. Nevertheless he gained 115 grams of weight in these five days. Clearly a phenomenon displayed by a normal man cannot be classed as a specific sign of disease.

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CERTAIN ASPECTS OF PULMONARY ABSCESS FROM AN ANALYSIS OF 210 CASES¹

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CERTAIN aspects of pulmonary abscess are presented as a continuation of the study of this disease at the Massachusetts General Hospital. Two hundred and twenty-seven cases occurring between 1909 and 1924 have been analyzed by one of us^{1,2}. The present series embraces 211 cases observed from 1924 to 1932. As of this number all but one has been followed to the termination in death or present condition from two to nine years after discharge, the discussion to follow is based on the 210 cases. For the unusual success in the follow-up we are indebted to Miss Eleanore A. Lewis and Mrs. Alice R. Coghlin.

Though the cases under discussion are all classed as lung abscess, the designation lung gangrene would be equally appropriate for the great majority of the series, inasmuch as in 192 cases the sputum is recorded as foul. No note as to the odor is recorded in 14 and the sputum was said not to be foul in four. There was no sputum in one case in which abscess was found at autopsy.

PREDISPOSING FACTORS

The etiologic importance of operations about the upper respiratory tract has increased. While one out of every three cases of abscess could be traced to such a procedure in the 227 cases occurring between 1909 and 1924, the proportion in the present series has risen to about one in two cases (117 of 210 cases, or 55.7 per cent). The operative procedures included the removal of tonsils and adenoids in 81 (38.6 per cent), the extraction of teeth in 26 (12.4 per cent) and an upper respiratory operation in 10 (4.8 per cent). The increase in the proportion of cases which follow operations about the upper respiratory tract may be ascribed to the more frequent performance of such operations in recent years. There are, in addition, 19 (9.0 per cent) due to other operations under a general anesthetic, making a total of 136 (64.7 per cent) referable to a previous surgical procedure. The etiologic factors in the remaining 74 (35.2 per cent) are less clear. In 48 (22.9 per cent) the onset was insidious and the cause undetermined. A more stormy onset in 17 (8.1 per cent) suggested pneumonia as a cause, but the evolution and grouping of initial symptoms were consistent with lobar pneumonia in only three instances. The abscess followed an upper respiratory infection in 5 (2.4 per cent).

In this series, 141 (67.1 per cent), or two out of every three cases, occurred under such circumstances as to make it reasonable to assume that

* Read at the Chicago meeting of the American College of Physicians, April 20, 1934

the abscess arose in consequence of access to the lung of infected material from the upper respiratory tract

SPECIAL DIAGNOSTIC MEASURES

Bronchoscopy Examination by this means should be considered in all cases with localized pulmonary suppuration. It is especially indicated when there is evidence of bronchostenosis for the purpose of establishing the presence or absence of a foreign body or tumor. Bronchoscopy was done on 72 cases in the present series. Inflammatory narrowing of a bronchus was thus established in 29 and a congested mucous membrane in 11. It is helpful in certain cases in more accurately localizing the abscess by the determination of the part of the bronchial tree from which pus emerges, but the expulsion of purulent material from one bronchus to another by cough may make it difficult to determine its source. In our experience, the method has not proved of value in the treatment of lung abscess in the absence of foreign body as a cause.

Lipiodol Insufflation Seventeen cases were investigated by means of lipiodol insufflation for the purpose of more accurate localization of the abscess. The number is small, as the site of the process can ordinarily be satisfactorily determined by other means. In nine of the cases, or about one-half, additional information of value was not obtained. There is, however, a small group of cases in which localization by roentgen-ray is uncertain on account of obscuration by the overlying shadow of the heart or the diaphragm. With improvement in roentgen-ray technic and the use of profile films in addition to anteroposterior views, lipiodol is seldom necessary for the localization of lung abscess. It is, however, of great value in the differentiation of lung abscess from bronchiectasis.

PROGNOSIS

Of the 210 cases, 73 (34.8 per cent) completely recovered, in 49 (23.3 per cent) the condition was improved, in 10 (4.7 per cent) the disturbance persists unabated, and 78 (37.1 per cent) died. Of 96 operated cases, 27 (28.1 per cent) recovered, 26 (27.1 per cent) improved, 5 (5.2 per cent) were unimproved and 38 (39.5 per cent) died. Of the 38 deaths following operation, we estimate that in 12 the fatalities were in part at least to be ascribed to the operative interference.

TREATMENT OF LUNG ABSCESS

From our review of the present series, certain comments may be made regarding the treatment. In making a decision regarding the most desirable course to pursue, it should be appreciated that there is a large group of cases in which the indications are on the borderline between conservative measures and surgical interference.

Conservative Treatment It is, in general, best to subject patients with lung abscess to a period of observation and investigation for the purpose of deciding upon the best course to pursue. In adopting an expectant policy and meanwhile using bed rest and postural drainage, it must be kept in mind that there is danger of extension of the suppurative process, of the development of multiple from a single focus, of empyema, of cerebral abscess and of septicemia. But in view of the hazards of surgery and the chance of recovery without radical measures, it, nevertheless, seems desirable first to give a fair trial to the simpler procedures. This regime is, in general, applicable only within the first two to three months of the illness and should be continued only so long as progress is favorable, as indicated by the amount and character of the sputum, the abatement of the toxemia and a diminution of the extent of the process by physical and roentgen-ray examination.

Recovery without Radical Treatment From previous experience, the chance of recovery without resort to operation was estimated at about one in every 10 cases.

In the present series the number of recoveries without resort to pneumothorax or surgery has risen to a considerably higher proportion. Forty-five (21.4 per cent) of the 210 were completely relieved of all indications of abscess. In addition, in seven the returns indicate restoration to health and capacity, but the presence of cough and scanty expectoration without foul odor, make it necessary to place them in a doubtful class. The expectation of relief may thus be estimated for the present series as about one in every five cases.

Information is desirable regarding the factors which may be expected to favor recovery without resort to radical measures and it is, in consequence, of interest to consider this recovered group more in detail, with respect to the (1) exciting causes, (2) previous duration and (3) site of the process.

The exciting causes in the 45 completely recovered cases were the removal of tonsils and adenoids in 21 (46.7 per cent), the extraction of teeth in seven (15.6 per cent), an upper respiratory operation in three (6.6 per cent), other operation under a general anesthetic in four (8.9 per cent), an upper respiratory infection in one (2.2 per cent), and pneumonia in two (4.4 per cent). The abscess was primary in seven (15.6 per cent). The percentage incidences of the various exciting causes correspond so closely in the recovered group and in the series as a whole that the nature of the exciting cause appears not to be of moment in influencing recovery without interference.

A short previous duration is one of the most important factors in favorably modifying the chance of recovery under medical observation. In considering the prospect of recovery in relation to a duration of two months or less in the series as a whole, we find that of 110 cases in this category, 34 (30.9 per cent), or about one in every three cases, recovered without other than conservative treatment. Though the expectation of recovery

without operation is thus largely confined to patients with a short previous duration of the disease, 11 cases recovered after a longer period of illness, including five cases of two to three months', one of four months', one of six and one-half months', three of 11 to 12 months' and one of 18 months' duration. The prospect of spontaneous recovery after a long previous duration is more favorable than analysis of the earlier series seemed to indicate, as in that series none of the cases with a previous duration longer than nine weeks recovered spontaneously.

The site of the process is of moment to the prospect for recovery without interference, and in this as in the previous series, a location at or above the root of the lung is relatively favorable, while lesions below this level are less promising. In general, also, it may be said that the symptoms due to the infection and the extent of the pulmonary process were less marked in the cases recovering without radical measures.

Neoarsphenamine in Treatment In view of the frequency with which neoarsphenamine is used in the treatment of lung abscess or gangrene, it is desirable to obtain more definite information regarding its merits. Fifty-five patients in the series have been treated with neoarsphenamine. Comparison of the results in this group with those in the series as a whole suggests that no favorable effect is to be ascribed to its use. Estimate of the value, if any, of the drug is complicated in a majority of the cases by the variability and, at times, by the length of the previous duration of the condition, before treatment was begun. There are, however, seven cases treated with three or more doses of neoarsphenamine within 13 to 21 days of the onset of the disease. Of these seven cases, two recovered completely and one died under medical care. Two of the remaining four were later subjected to pneumothorax and two to a rib resection and drainage. In the last two mentioned cases, in spite of the institution of treatment in one within 16 days, in the second within three weeks after onset, there was extension of the process by roentgen-ray before operation was done. Neither in the clinical aspects nor in the final results, is there evidence that the administration of neoarsphenamine favorably modified the course of the disease.

COLLAPSE THERAPY

Brilliant results in the application of collapse therapy to the treatment of pulmonary tuberculosis merited the hope of its successful use in the management of lung abscess. The suppurative lesions differ, however, in that drainage is the essential factor in healing, while rest is of paramount importance in recovery from tuberculosis.

Pneumothorax in Treatment Treatment by artificial pneumothorax was attempted in 22 patients, but failed in six because of adhesions. Partial collapse was obtained in four and complete collapse in 12. Of these 16 cases nine may be regarded as failures so far as this method of treatment is concerned, as the patients later came to operation. Of the remaining seven,

one completely recovered, three improved and three died. Thus, in our experience, there are only four cases in which benefit was apparently derived from the treatment and the advantage in this small group is offset by three patients in whom the procedure was certainly or probably harmful. All three developed empyema under the treatment and of the three, two died. Though empyema occasionally complicates untreated abscess, its occurrence after artificial pneumothorax in three of 16 cases suggests that the procedure was largely responsible. In our four favorable cases, improvement or complete recovery might have taken place without resort to artificial pneumothorax. In rare instances, as in one case in the series, the artificial pneumothorax makes it possible to localize an abscess, the site of which is otherwise uncertain.

Artificial pneumothorax has proved disappointing as a therapeutic measure. Its use entails the danger of empyema, which may in turn make surgical measures difficult or impossible.

Phrenic Nerve Operation The induction of diaphragmatic paralysis has been followed by recovery in isolated instances of lung abscess. The procedure would seem theoretically likely to be most serviceable with a lesion at the base, but there is always the possibility that bronchial drainage will be hindered rather than favored by this method. It was used as the sole surgical measure in only two cases in this series. In one instance, a man of 34, with a history of cough and foul sputum amounting to 12 to 15 ounces daily for a year, and a process at the right base, the patient died of hemorrhage about six weeks after the crushing of the right phrenic nerve. In the second case, a man of 58, with an abscess involving the middle and right upper lobes, there was no improvement following a right phrenic nerve operation and the patient committed suicide one and one-half years later.

Thoracoplasty Thoracoplastic collapse therapy may be considered with multiple, diffuse, unilobar or unilateral abscesses of such a previous duration that spontaneous recovery cannot be expected. In adopting this method, it is desirable to exclude cases in which there is a prospect of complete recovery following open drainage or lobectomy. Thoracoplasty has the merit of a relatively low operative mortality and the disadvantage that by this means alleviation rather than cure may be expected. Of 15 cases subjected to thoracoplasty, in three a complete posterior operation was done, for diffuse involvement of the right upper lobe in two, and for involvement of the whole right lung in one. Of these three, the operation resulted in complete recovery in two and improvement in one. A partial thoracoplasty was done on the remaining 12 cases, with removal of parts of the ribs in the neighborhood of the involved regions. The operation involved the upper six ribs posteriorly in five cases, the lower six ribs posteriorly in one case, and the ninth to the eleventh ribs inclusive in one, with complete recovery in one case, improvement in three, lack of improvement in two and death in two. Of four patients subjected to apicolysis, one completely recovered, two improved and one died. In the remaining case operated

upon, the condition remained the same, in spite of both a posterior and an anterior thoracoplasty of the upper six ribs and apicolysis

DRAINAGE OPERATIONS

Drainage of Empyema Complicating Lung Abscess The simplest surgical procedure is drainage of empyema when it occurs. Drainage with or without rib resection for empyema secondary to lung abscess may successfully evacuate the lung abscess. Of 13 cases in this group five recovered, one was improved and seven died.

Surgical Drainage of Lung Abscess Operative interference on the abscess is to be considered after a preliminary trial of rest and postural treatment. Lesions near the chest wall are relatively favorable for surgical drainage. The results are most satisfactory when the abscess is single, but multiple circumscribed lesions may be successfully drained. Diffuse lesions with multiple cavities are in general not suitable for surgical drainage. In recent years the cautery has been used to unroof the abscess cavity. Continuance of foul sputum after operation indicates an undrained pocket. Of 56 cases subjected to open drainage, 16 (28.6 per cent) recovered, 16 (28.6 per cent) were improved, 2 (3.6 per cent) were the same after operation and 22 (39.5 per cent) died.

Cautery Lobectomy In addition to the opening of the abscess, a more extensive operation may be necessary for the removal of necrotic parts of the affected lung. Of eight such cases, two recovered, three were improved and three died. A complete lobectomy was attempted in two patients, in one by means of the cautery and in the other by exteriorization, and both died.

SUMMARY

The importance in etiology of operations about the upper respiratory tract has increased from one out of every three cases (1909–1924) to one out of every two (1924–1932). Though bronchoscopy is helpful in certain cases in accurately localizing the abscess, it has not proved of value in treatment in the absence of foreign body as a cause. Lipiodol is seldom necessary for the localization of lung abscess, but is of great value in the differentiation of lung abscess from bronchiectasis. The expectation of complete recovery from lung abscess under conservative treatment has risen from about one in every 10 cases (1909–1924) to about one in every five (1924–1932). A short previous duration is one of the most important factors in favorably modifying the chance of spontaneous recovery, which may be estimated at about one in every three cases with a duration of two months or less. A small proportion of patients recover under conservative management after the disturbance has lasted from two to 18 months. Mild and inextensive processes situated at or above the lung root are relatively favorable for recovery without interference.

Of therapeutic measures in our experience evidence is lacking that neoarsphenamine favorably modifies the course of the disease. Regarding collapse therapy, artificial pneumothorax has proved disappointing and entails the serious risk of inducing empyema. Thoracoplasty may be used in carefully selected cases and is at times successful. Suppurative pulmonary lesions differ from tuberculosis with respect to the application of collapse therapy in that drainage is an essential factor in promoting healing. Drainage of a complicating empyema may successfully evacuate a pulmonary abscess. Open drainage of lung abscess is indicated in suitable cases after a trial of rest and postural treatment. Partial cautery lobectomy may be necessary for the removal of necrotic parts of the affected lung.

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THE NATURE OF PELLAGRA · A CRITIQUE

By JAMES S. McLESTER, F A C P, *Birmingham, Alabama*

IN THE first few years of the present century there suddenly appeared in the Alabama Insane Hospital a new disease of unknown nature, the salient characteristics of which were a violent dermatitis of the exposed parts, sore mouth, profuse diarrhea, grave nervous disturbances, and high mortality. The disorder was recognized finally by Searcy, a member of the resident staff, as identical with the pellagra described in the European literature. The rapid spread throughout the Southeastern states of this new and highly fatal disease excited general interest, and concerted efforts were made to determine its cause. Notable among these, but almost forgotten now, was the work of the Thompson-McFadden Commission which during a period of two years made an intensive study of the inhabitants of six mill villages near Spartanburg, South Carolina. The resulting report not only discussed the relationship of certain foods to pellagra but gave interesting data suggesting the conclusion that pellagra is essentially a house disease and that all of the cases of that area could be traced to one focus. A few years later came the carefully planned work of Goldberger who, starting with the prevalent belief that the disease is due to dietary faults, studied the food habits of those people among whom pellagra most frequently appeared, particularly the inmates of orphanages, asylums and prisons. He was signally successful in eliminating this disease, by means of an improved dietary, from two orphanages and an insane asylum in which it had previously been endemic, but the achievement upon which his conclusions largely were based was the production in a group of convicts fed upon deficient diets, of a disease which he and his associates regarded as pellagra. Goldberger's final conclusion that pellagra is due to a specific dietary fault, lack of vitamin G, is now generally accepted the country over, except, it should be noted, in those areas in which the disease occurs with greatest frequency. There, opinion is divided. There are, therefore, two views as to the nature of pellagra, the one, that it is a specific avitaminosis, the other, that there are operative in its causation factors other than a single dietary deficiency. To present this last view is the object of this report.

Two considerations render the avitaminosis theory difficult of acceptance: first the apparent impossibility of invariably relating pellagra to faulty diet or of correcting the disorder by dietary means, and second its epidemiologic characters. The relationship of pellagra to faulty diet is not always clear. True, most pellagrins are poor and their food habits are grievously at fault, but this is not universally true. Time and again I have seen pellagra in a person of ample means whose table was abundantly supplied with the proper

foods, who was apparently well nourished, and in whose diet no gross fault could be detected. Other physicians report similar observations.

I have been deeply impressed also by the difficulty frequently encountered of effectually influencing the course of pellagra by dietary means. We not infrequently see cases in which a balanced ration rich in the vitamin B complex with an abundance of yeast exerts no effect on the fatal course of the disease. The most satisfactory experience I have had has been with liver, at times it works wonders, but occasionally it, too, is of little or no influence. If we conclude that nutritive failure is the sole cause of pellagra, then we must assume that structural damage of such a permanent nature is done that in many instances restoration of the missing factor is of no avail. In most deficiency diseases, notably in scurvy, and in the polyneuritis of fowls correction of the dietary fault accomplishes promptly beneficial, sometimes graphic, results. Not so in pellagra, the result of treatment is much less certain. (Figures 1 and 2)

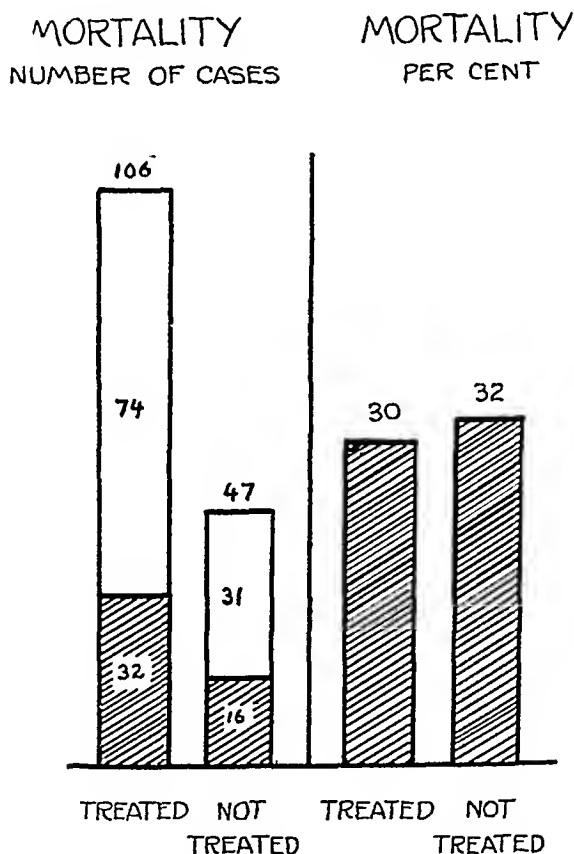


FIG 1 Pellagra Hillman Hospital (1920-1933)

The epidemiologic features of pellagra likewise are difficult to reconcile with simple avitaminosis. To those of us who saw this disease when it

AVERAGE DAYS IN HOSPITAL

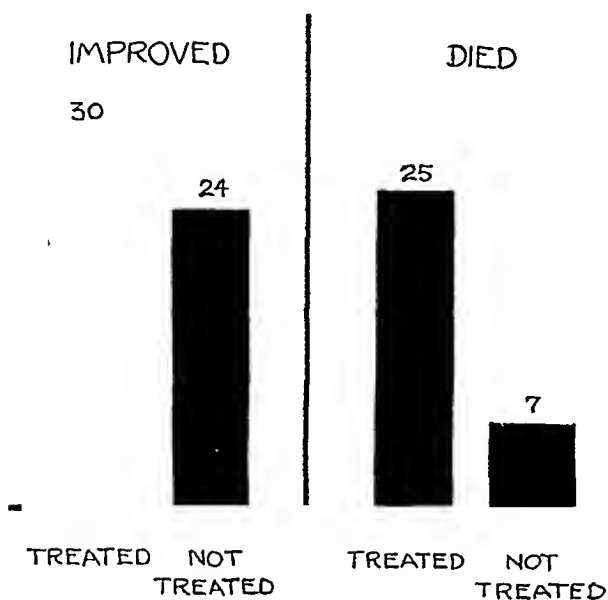


Fig 2 Pellagra Hillman Hospital (1920-1933)

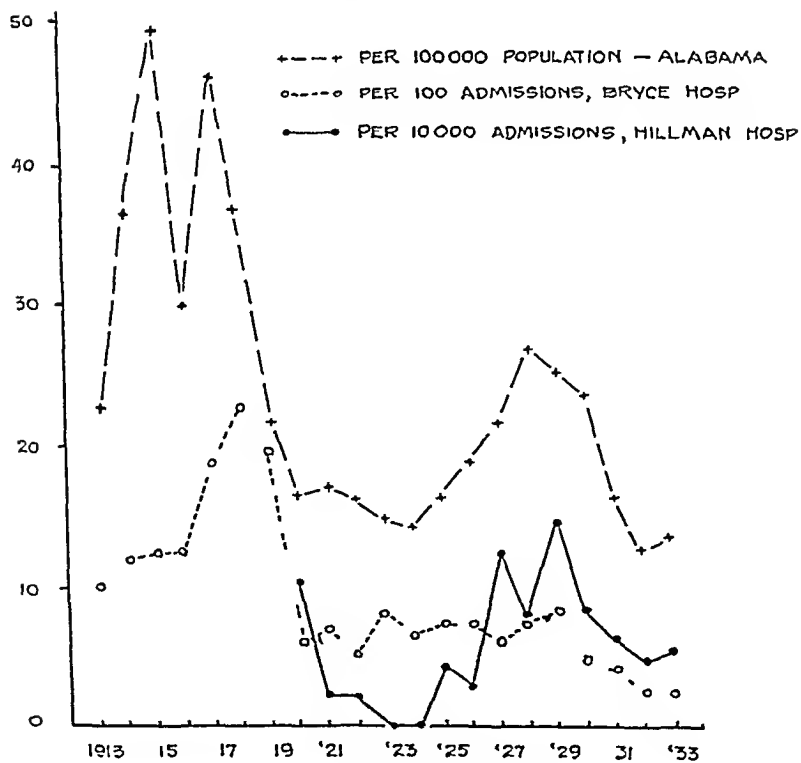


Fig 3 Pellagra death rates

first appeared, and who have watched its spread, there come questions that are difficult to answer. Why did pellagra come with such extreme suddenness and spread like a prairie fire throughout the Southeastern states? What is the explanation of the wide fluctuations in the incidence of this disease since its first appearance in America, with, at first, an exceedingly high death rate and then, following successive outbreaks, a steady lowering of the mortality? (Figure 3) No parallel changes in the food habits of the people have been observed.

Witness the manner in which pellagra, both as individual cases and in epidemic form, seems to spread from definite foci, whether the focus be a single house, a county or a state (Figure 4). The data of the Thompson-McFadden Commission indicate that, among people of the same economic status, the hazard of developing pellagra is greatest, vastly so in a house which has harbored a previous case, less in the house next door, and least of all in houses at a distance. Likewise, statistics show that in Alabama the disease has been much more prevalent in neighboring counties (figure 5), and that in the Southeastern part of the country it has been more prevalent in contiguous states (Figure 6). Why did this disease exhibit itself in its most violent form among the crowded inmates of orphanages, insane hospitals and prisons? There was no sudden change in the dietary habits of the population, nor were the rations of the affected institutions radically different from what they always were. The Alabama Insane Hospital, for instance, has always maintained large farms and its food supply, which includes milk, vegetables and meat, has remained essentially the same for the past 50 years. Why was pellagra epidemic from 1905 to 1909 in the insane hospitals of Alabama, Georgia and South Carolina, while, during that same period, no case appeared in St. Elizabeth's at Washington or in the insane hospitals of New York state? The food of all of these asylums North and South, according to the investigations of Partlow, Superintendent of the Alabama Institution, was not essentially different. These features of the epidemiology of pellagra remind one of such communicable diseases as influenza, measles and smallpox rather than of a true deficiency disease.

The experiments of Goldberger and Wheeler were well planned and admirably executed, but examination of their data permits one to question, I feel, the accuracy of their conclusions. Eleven volunteer convicts were given a grossly deficient diet and upon the appearance of certain skin lesions in six of these the diagnosis of pellagra was made. These six men developed a dermatitis upon the scrotum which Dr. Goldberger and the associated dermatologists accepted as evidence of pellagra. Except in two instances, one a dermatitis upon the dorsum of the hands, and the other an erythema of the neck, there was no eruption on the exposed areas. A recognized characteristic of the skin lesion of pellagra is that it comes first, and as a rule solely, upon the exposed parts, notably the forehead, the front of the neck and the dorsum of the hands, and that these lesions appear most quickly and in most violent form when the patient is exposed to the direct

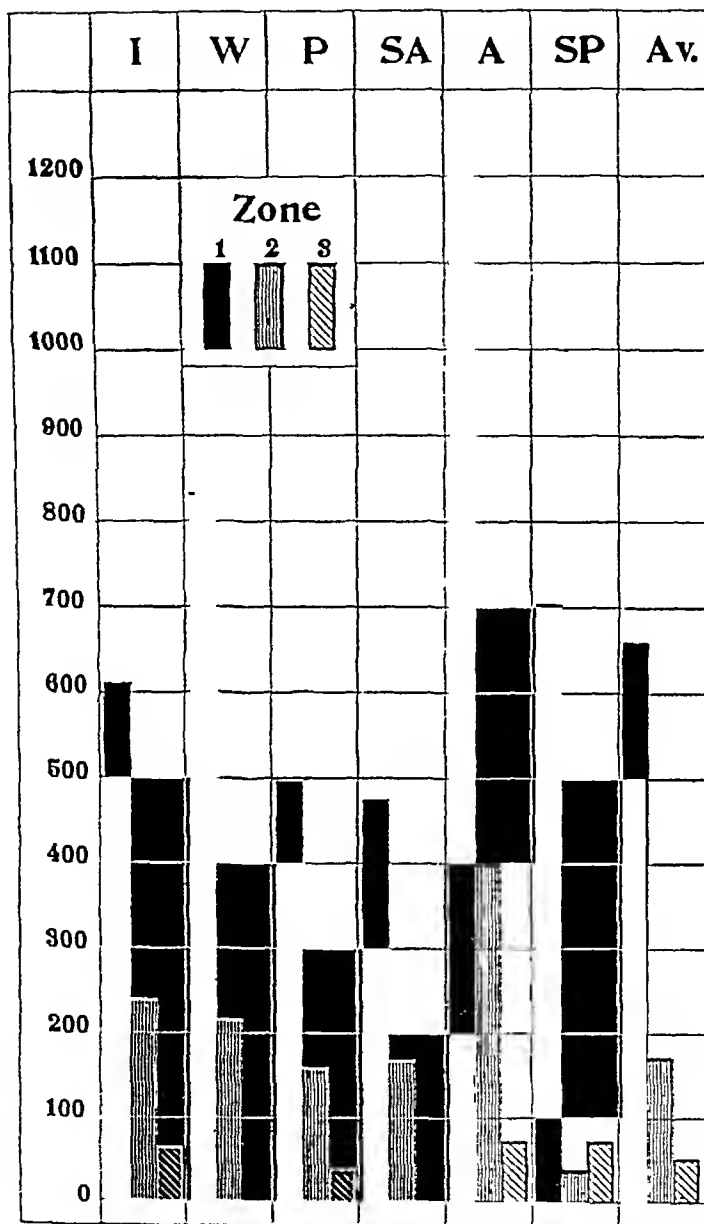


FIG. 4 Location of domestic incident cases per 10,000

The black columns indicate the incidence of new cases of pellagra among persons living in the same house with a preëxisting case. The columns striped vertically indicate the incidence in the population living next door. The columns striped obliquely indicate the incidence in the population living within the respective village, but farther away than next door from a preëxisting case of pellagra. (Reprinted from Siler, Garrison and McNeal,¹ by permission of the Archives of Internal Medicine.)

Hospital in Birmingham, in only one was a genital lesion recorded and this was not the primary skin manifestation. Goldberger told of a few cases exhibiting scrotal lesions quoted from South Africa and of two in America, in addition to certain subsequent observations made by his associate Dr Wheeler, but he adds, "it remains a fact, however, that the genital lesion whether early or late is a somewhat unusual one." Our experience in Alabama is that it is an extremely unusual one. It is inconceivable to me that these men, working as they were, in the fields of a Mississippi plantation under a midsummer sun should have developed their first lesion on a protected part such as the scrotum, and (except in two instances) shown no lesion whatever upon those parts of the skin exposed to the direct rays of

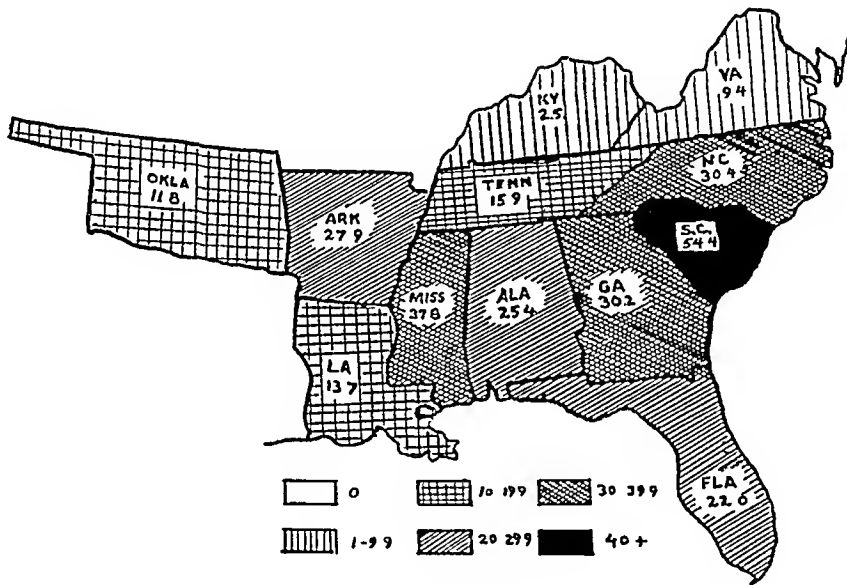


FIG 6 Pellagra death rate (1929) per 100,000 population

the sun. The subjects of this experiment, as the report would indicate, experienced the ill effects of a grossly lacking diet, but that they had pellagra is, I believe, open to reasonable doubt.

The work of Goldberger and his associates has been of inestimable value in demonstrating that faulty diet plays a part in the production of pellagra and in pointing the way toward improvement. I am voicing the opinion, of many observant physicians, however, notably those of the hospital in which pellagra has been studied longest, when I express the belief that the true nature of this disease has not yet been fully explained and that a re-examination of the entire problem would be profitable. Unquestionably nutritional failure plays a part, for most cases, though not all, are associated with faulty diet and most patients, though not all, get well when properly fed, but the assumption that a single dietary fault is the cause of the disease is far from satisfactory.

What, then, are the possibilities? Two, in the order of their prominence, come immediately to mind. First, that pellagra is the expression of a multiple food deficiency, this could be the result simply of a grossly deficient diet or of some physiologic defect which prevents the proper utilization of food, or indeed, of a combination of the two. Second, that directly or indirectly, an infective agent is concerned in its causation. I do not regard as entirely disproved the belief that pellagra is due to nutritional failure plus the invasion of a specific microorganism. The former conceivably could prepare the way for the latter. The high mortality when the population was first attacked and the gradual lessening in severity, accord with our experience in epidemics of infectious disease, and, since pellagra appears to be a house disease, if we accept tentatively the infectious theory, then there is much which would suggest that this infection is carried by an intermediate host. An infectious nature would explain its sudden appearance and rapid spread, while necessity for a vector would explain its appearance most often among conditions under which personal cleanliness is difficult and in institutions in which over-crowding is the rule.

Such considerations incline me to the belief, notwithstanding the careful work that has gone before, that the last word regarding the nature of pellagra is yet to be said.

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THE RECENT TREND TOWARD A DIFFERENTIATION BETWEEN ALLERGY AND IMMUNITY, AND THE RELATIONSHIP TO CLINICAL MEDICINE *

By LAY MARTIN, M D , F A C P , *Baltimore, Maryland*

FOR many years writers have been promulgating the idea that allergy is an integral and essential part of the process of immunity. It has been taught and almost universally believed that the local and general response of allergy has been a necessary, although at times, a dangerous defense reaction in the immunological mechanism. In the past few years a small number of men have questioned this belief and their queries have led to investigations, the results of which point strongly to the idea that allergy and immunity can be dissociated and that the former is not necessary for the proper functioning of the latter.

The object of this paper is to develop the theoretical and investigative facets of the subject and to present to the clinician what is an extremely important, but as yet insufficiently accentuated, problem in medicine.

In medical literature it would be difficult to find more confusion than that which obtains in the interpretation of such terms as allergy, anaphylaxis, hypersensitivity and immunization. At the onset it will be necessary to make clear what meaning and usage will be made of these words in the following exposition.

Allergy is used to represent that delayed reaction which follows the reception into tissues of an antigen to which the tissues are sensitized. It is characterized by edema, inflammation, tissue destruction and necrosis. It is typified by the tuberculin reaction of Koch and the Arthus phenomenon.

Anaphylaxis is used to describe that immediate reaction which takes place in smooth muscle when its sensitized cells come in contact with the antigen to which they are sensitized. It is entirely different in action from the allergic reaction described above and may take place in the water bath by the Schultz-Dale method after all the blood has been removed through perfusion. In the intact animal it is typified by the acute shock of a guinea pig sensitized to a protein, which has received intravenously a small dose of the specific antigen. The most striking pathologic change is found in the marked distention of the lungs brought about by the spasm of the small bronchiolar musculature, tissue necrosis does not occur.

Hypersensitivity (or hypersensitiveness) is used to express that state of an animal which is allergic or anaphylactic or both. As will be shown below, both states may exist in the same animal and it may be possible temporarily to remove one and leave the other intact. It should only be used as a

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.
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descriptive term when it is not necessary to designate in more detail the type of sensitization

Immunization is the word which has done most to cloud the issue. It has been loosely used to describe a number of procedures and of states produced by such procedures. It will be used here to describe the process of making an animal resistant to bacterial invasion or to the effects of bacterial toxin. An immunized animal is one which can withstand bacteria or toxic products which would greatly distress or kill a control animal. It is not used to represent that state which causes an animal to react with dangerous smooth muscular spasm, or inflammation and tissue destruction, to bacteria or a foreign soluble protein, which are non-toxic to normal animals but to which it is sensitized. As the subject is desperately in need of clarification, further discussion, in the hope of simplification, seems permissible.

The early investigators of the effects of diphtheria toxin and toxoid showed that animals could be made immune by injecting the filtrate in gradually increasing amounts. At an early stage substances appeared in the blood stream which neutralized the toxin in measurable amounts. These protective substances were called antitoxins or immune bodies. When toxin was injected into animals properly immunized no reaction occurred and the animals appeared undisturbed.

It was also found that the injection into animals of materials, such as egg white and foreign sera, promoted the production of antibodies which reacted, *in vitro*, with their specific antigens and neutralized them in a way analogous to the toxin-antitoxin combination. The reaction within the animal in this case (when the antigen and antibody united) was not the quiet, harmless union of the diphtheria toxin-antitoxin but an explosive, dramatic affair which more often than not killed the sensitized animal. As antibodies were produced after both the bacterial toxin and the non-toxic protein were injected and as both gave similar test tube reactions, they were both looked upon as immune bodies. That they reacted within the intact animal in different ways was quite evident but both reactions were looked upon as the results of immunization. It was held that the reaction of humoral antibody with the antigen was the method by which the cells were protected against the protein coming in contact with them and causing even greater damage. To call an occurrence such as that which takes place when an innocuous material, egg white, penetrates into the body, an immune reaction is sardonic humor indeed. These animals are not immune they are hypersensitive. At this time it is of interest to recall a portion of the excellent investigation of Neill, Sugg and Richardson¹. They have observed that if guinea pigs are repeatedly injected with diphtheria toxin or toxoid they not only develop such antibodies as antitoxin but that after they have been Schick negative for varying periods of time they become hypersensitive. At this time an intravenous injection of the toxoid will produce anaphylactic shock. In animals which have been injected in the usual

manner, no such reaction occurs. It is apparent that these animals were immunized against toxin and later became hypersensitive. To say that they became hypersensitive to the protein of the toxin and not to the toxin itself would seem to beg the question as it is quite probable that these are one and the same thing. These men succeeded in desensitizing some of the hypersensitive animals and their immunity to the toxin remained.

This discussion of anaphylaxis and immunity is perhaps somewhat apart from the main topic, namely the dissociation of allergy and immunity, but it is included as it is quite possible that both forms of hypersensitivity represent responses to a fundamental change in the animal's mechanism.

The difference between the methods of production of the hypersensitive states, anaphylaxis and allergy, is a point of interest. Some investigators find that after intracutaneous injections of bacterial protein or bacteria, they are able to demonstrate allergy but not anaphylaxis, others find that both reactions will occur. Following the intravenous injection of the same materials some investigators find only the anaphylactic response, others see both. The variable in this rather unsatisfactory state of affairs seems to be the dosage and repetition of dosage, of the sensitizing agent. At the present time it appears that when a small dose is given repeatedly, intracutaneously or intravenously, there will be produced respectively an allergic or an anaphylactic type of response. The question is, however, not satisfactorily answered and awaits further investigation. Tables 1 and 2 are included because they indicate the data presented in some of the more recent publications. Study of them will show that there are at least a few points remaining to be clarified.

Robert Koch² made the observation that if the tuberculous animal was reinjected with tubercle bacilli a local response developed which was evidenced by edema, inflammation, necrosis and ulcer formation with final healing. The same was true if tuberculin was injected instead of the virulent organisms with the exception that there was rarely ulcer formation. The reaction was a delayed one and reached its culmination in 24 to 48 hours. It came to be known as the *tuberculin reaction* or Koch phenomenon. Von Piquet³ became greatly interested and referred to it as allergy (meaning altered tissue reactivity). Subsequently a great many investigations were undertaken and through the excellent demonstrations of Romer,⁴ Baldwin,⁵ Krause⁶ and numerous others, it became widely believed that the tuberculin reaction was to be found only in the presence of a tubercle brought about by infection. Later it was demonstrated by Petroff and Stewart⁷ that a sufficient dose of dead tubercle bacilli given parenterally would produce the same result.

It has also been abundantly shown that in those instances in which there was both infection and allergy the animal was completely resistant to reinfection. Later it was shown that resistance to reinfection and allergy was found after inoculation with heat-killed bacteria and also with an avirulent strain isolated by Trudeau, called R₁.

TABLE I

Immune and Hypersensitive States Induced by Intravenous or Intraperitoneal Inoculation

| Investigators | Year | Animal | Sensitizing agent | Testing agent | Active sensitization | | | After desensitization | | Passive sensitization | | |
|------------------------------------|------|-----------------|---|------------------------------|----------------------|---------|----------|-----------------------|----------|-----------------------|---------|----------|
| | | | | | Anaphylaxis | Allergy | Immunity | Allergy | Immunity | Anaphylaxis | Allergy | Immunity |
| Baldwin ²⁵ | 1910 | Guinea pigs | Tuberculin | Tuberculin | + | 0 | 0 | | | | | |
| Baldwin ²⁶ | 1910 | Guinea pigs | Tubercle B | Tuberculin | + | + | + | | | | | |
| Austrian ²⁷ | 1913 | Rabbits and g p | Tuberculin | Virulent tubercle B | + | 0 | 0 | | | | | |
| Krause ²⁸ | 1916 | Guinea pigs | Tuberculin | Virulent tubercle B | + | 0 | 0 | ± | 0 | | | |
| MacKenzie ¹⁸ | 1925 | Rabbits | Heat killed pneumococci | Heat-killed pneumococci | + | 0 | + | | | | | + |
| Zinsser and Grinnell ¹⁹ | 1925 | Guinea pigs | Streptococcus | Streptococcus filtrate (a) | | + | | | | | | |
| Zinsser and Mueller ²⁹ | 1925 | Rabbits and g p | Defatted tubercle B | Tuberculin (a) | | + | | | | | + | |
| Zinsser and Grinnell ⁴⁰ | 1927 | Guinea pigs | Pneumococcus autolysate | Pneumococcus autolysate (a) | | + | | 0 | | | 0 | |
| Tillett | 1928 | Rabbits | Heat-killed pneumococcus | Virulent pneumococcus | | | + | | | | | + |
| Tillett | 1928 | Rabbits | Nucleoprotein of pneumococcus | Virulent pneumococcus | | | 0 | | | | | |
| Derick and Swift ³⁰ | 1929 | Rabbits | Non hemolytic streptococcus | Non hemolytic streptococcus | + | 0 | | | | | | |
| Ender ⁴¹ | 1929 | Guinea pigs | Heat killed tubercle B | Tuberculin | + | + | ± | + | ± | + | 0 | |
| Ender ⁴¹ | 1929 | Guinea pigs | Heat-killed tubercle B | Carbohydrate fraction | + | 0 | ± | 0 | ± | + | 0 | |
| Bull and McKee ¹ | 1929 | Rabbits | Pneumococcus heat killed or nasal infection | Pneumococcus autolysate | + | + | + | | | | | |
| Rieb and Brown | 1930 | Rabbits | Heat-killed pneumococcus | Heat killed pneumococcus | + | + | + | | | | 0 | + |
| Juhanelle ¹ | 1930 | Rabbits | Heat-killed pneumococcus | Heat killed pneumococcus (b) | 0 | + | + | | | | 0 | 0 |
| Juhanelle ¹ | 1930 | Rabbits | Pneumococcus nucleoprotein | Pneumococcus nucleoprotein | 0 | + | 0 | | | | + | 0 |
| Branch and Cuff ³ | 1930 | Guinea pigs | Heat killed tubercle B | Tuberculin | + | + | + | | | | | |
| Clawson ³⁹ | 1932 | Rabbits | Heat killed streptococcus | Virulent streptococcus | + | 0 | + | | | | | |
| Seibert ²⁰ | 1932 | Rabbits and g p | Purified tuberculin | Purified tuberculin | + | + | | | | | + | |
| Stillman and Goodner ²³ | 1933 | Rabbits | Heat killed pneumococcus | Heat killed pneumococcus | + | + | | | | | | |

Note

(a) Intraperitoneal sensitization

(b) Mice only used to demonstrate passive transfer of immunity

Krause and numbers of other experienced workers have become convinced that the allergy which accompanies infection is one of the strongest protective weapons at the command of the body. This is the widely known statement, "We believe that specific tubercle immunity occurs through a fixation of germs that result from the operation of the allergic reaction"⁶ He believed with Baldwin "The inflammatory reaction following inoculations of immune animals is the important thing. We are justly entitled to the opinion that cell accumulations about the bacilli are performing the duty of dissolving them or retarding their growth"⁵ This theory was strengthened by the investigations of Willis⁸ who found that in the normal animal, bacteria left the field of inoculation in a matter of minutes and could be demonstrated in the regional lymph glands in a few hours. In the infected (allergic) animals no organisms were found in the glands until several days had elapsed. This work has recently been corroborated by Freund⁹ and

TABLE II
Immune and Hypersensitive States Induced by Intracutaneous Inoculation

| Investigators | Year | Animal | Sensitizing agent | Testing agent | Active sensitization | | | After desensitization | | Passive sensitization | | |
|-----------------------------------|------|-----------------|---|---|----------------------|---------|----------|-----------------------|----------|-----------------------|---------|----------|
| | | | | | Anaphylaxis | Allergy | Immunity | Allergy | Immunity | Anaphylaxis | Allergy | Immunity |
| Koch | 1890 | Guinea pigs | Tubercle B | Tuberculin | | + | + | | | | | |
| Calmette and Guerin ²⁶ | 1924 | Cattle | BCG | Virulent bovine tubercle B | | + | + | 0 | + | | | |
| Dochez and Sherman ⁴ | 1925 | Rabbits | <i>Streptococcus scarlatinae</i> filtrate | Live and killed organisms and filtrate | | + | | | | | | |
| MacKenzie ¹⁵ | 1925 | Rabbits | Pneumococcus nucleoprotein | Pneumococcus nucleoprotein | 0 | + | 0 | | | | | |
| Zinsser and Mueller ³² | 1925 | Guinea pigs | Virulent bovine tubercle B | Tuberculin | | | | | | | + | |
| Dochez and Stevens ¹³ | 1927 | Rabbits | <i>Streptococcus erysipellae</i> filtrate | <i>Streptococcus erysipellae</i> filtrate | | + | | 0 | | | | |
| Bull and McKee ⁴ | 1927 | Rabbits | Intranasal infection with pneumococcus | Pneumococcus autolysate | + | + | + | | | | | |
| Goodner ²³ | 1928 | Rabbits | Heat killed pneumococcus | Virulent pneumococcus | | + | + | | | | | |
| Derick and Swift ²⁰ | 1929 | Rabbits | Non hemolytic streptococcus | Non hemolytic streptococcus and the nucleoprotein (a) | + | + | + | | | | | |
| Martin and Hill ¹⁹ | 1929 | Guinea pigs | Heat-killed and virulent pneumococci | Heat killed pneumococci | | + | | 0 | | | | |
| Julianelle ¹ | 1930 | Rabbits | Heat killed pneumococci | Heat killed pneumococci (b) | | + | + | | | 0 | | 0 |
| Julianelle ¹ | 1930 | Rabbits | Heat killed pneumococci | Nucleoprotein of pneumococcus (b) | | + | 0 | | | + | | 0 |
| Branch and Cuff ²⁵ | 1930 | Rabbits | Heat killed tubercle B | Heat killed tubercle B (c) | + | 0 | + | | | | | |
| Seibert ³⁰ | 1932 | Rabbits and g p | Purified tuberculo-protein | Purified tuberculo-protein | | + | 0 | | | + | | |
| Clawson ²² | 1932 | Rabbits | Heat killed streptococcus | Virulent streptococcus | | + | 0 | | | | | |
| Sabin et al. ¹ | 1933 | Rabbits and g p | Tuberculo-protein | Virulent tubercle B | | + | 0 | | | | | |
| Friedenwald et al. ¹⁴ | 1933 | Guinea pigs | R ₁ tubercle B | Virulent tubercle B | | + | + | 0 | + | | | |
| Rich et al. ⁴⁵ | 1933 | Rabbits | <i>Treponema pallidum</i> | <i>Treponema pallidum</i> | | + | 0 | | | | | |
| Rich et al. ¹ | 1933 | Rabbits | Heat killed pneumococci | Heat killed pneumococci | | + | + | 0 | + | | | |

Note.

(a) Non hemolytic streptococcus not a lethal organism

(b) Mice only used to demonstrate passive transfer of immunity

(c) Intramuscular inoculations

complements the observations of Koch who noticed that the regional lymph glands of the reinfected animal did not become enlarged. Along the same line it is important to report the investigations of Opie¹⁰. He was able to show that none of the egg white, which was injected into the skin of an animal sensitized to it, reached the blood stream, but all was precipitated in the localized Arthus reaction. He believed that the precipitate acted as an irritant and caused the inflammation. This is quite different from the conception of Krause, who believes that the inflammation is a direct result of the union of antigen and sensitized cells.

Coming from such excellent sources the idea gained credence that the allergy found in any bacterial disease is part of the defense reaction of the

body Among others, Tsuda,¹¹ Cannon and Pacheco¹² and Menkin¹³ have published studies which have added to the weight of this belief Tsuda states that if specific organisms are injected into sensitized tissue and "if immunity is sufficiently enhanced, the injected cocci at the injected site show the phenomenon of agglutination in the form of follicular clumps and aggregations of microorganisms" He also states that the injected bacteria showed such evidences of degenerative change as swelling, poor staining, and inequality in size This work was extended by Cannon and Pacheco who found that staphylococci injected into specifically sensitized skin areas tended to agglutinate and clump more readily than in normal animals They believed that this was helped by the inflammatory reaction and in this they tended to agree with Menkin He believes that it is due to the inflammatory reactions—specific or non-specific—that a barrier is formed and bacteria are held at the seat of inoculation From his studies he gained the impression that there is an increased permeability of capillaries in areas of inflammation and that the lymphatics in such fields become obstructed He demonstrated that foreign particles, when injected intravenously, tend to accumulate in these areas and that if they are injected locally, they are held there He believes that the increased capillary permeability is the reason for the first finding, and the obstructed lymphatics for the second His work is excellent but in dealing with the question of antigen in sensitized tissue (allergic reaction) his theories are open to question A typical allergic reaction does not become fully developed until a few hours after inoculation and it cannot be this delayed reaction which is holding the antigen in check, for in the normal animal, as Willis⁸ has shown, the dispersal of bacteria takes place in a matter of minutes What occurs to hold bacteria there in the immune animal is an important point in the differentiation of allergy and immunity If it is not allergy, what is it? Before trying to answer this question other conditions must be considered

As is shown above there is considerable evidence that the allergic response is found in close association with immunity and there is, furthermore, much evidence which might incline one to believe that the reaction is an integral part of immunity However, in spite of this apparent union there is no proof that in the immune allergic animal the later reaction is essential to the immunological processes, that is, that the edema, inflammation and tissue destruction are essential and that immunity cannot exist in the absence of allergy

There are a number of observations which cause one to point an accusing finger at the untoward results of allergic reaction and regard it as a dangerous and perhaps unnecessary companion It is commonly accepted that many of the characteristics of disease entities are based on hypersensitive phenomena Pleurisy and pericarditis in tuberculosis are commonly accredited to hypersensitivity and there is much evidence that the establishment of this sensitization sets the stage for the development of meningitis and generalized miliary tuberculosis following ulceration of foci in the same

disease There is evidence that pneumonia develops in animals which have been sensitized to bacteria and soluble proteins (Sharp and Blake,¹⁴ Fried¹⁵) This has been shown either following intratracheal injection of pneumococcus autolysate into rabbits sensitized with pneumococci or by direct pulmonary injection of horse serum into rabbits specifically sensitized It is quite possible that tuberculous pneumonia is an allergic reaction There is much favorable criticism of the idea that the rash of scarlet fever, the joint involvements in rheumatic fever and the glomerular nephritis associated with lymphoid disease, are the result of allergic reaction It seems quite likely that the intestinal hemorrhages of typhoid fever are brought about by the action of specific antigen on the sensitized lymphatic tissue In fact, in the whole gamut of diseases it is possible to point out destructive lesions and frequently fatal terminations which are quite probably the result of allergic response Therefore, it would seem of essential importance to attempt an investigation, planned to demonstrate conclusively whether allergy is an integral part of immunity and if not, whether the animal can recover from infection more easily and promptly in its absence

Bouquet and Negre¹⁶ in 1928 presented the case for the French investigators in tuberculosis and stated "Immunité et hypersensibilité sont donc deux états distincts et indépendants des organismes infectés par le bacille de Koch"

Arnold Rich¹⁷ was the first clearly to analyze the situation and he has set a standard of excellence and ingenuity in investigation which will be difficult to surpass At the onset it should be stated that immunity to various bacteria has been established in a number of species of animal by MacKenzie,¹⁸ Zinsser,¹¹ Swift,²⁰ Julianelle,²¹ Tillett,²² Goodner,²³ Bull and McKee,²⁴ Rich²⁵ and numerous others Practically any method which permits sufficient numbers of virulent or heat-killed organisms to penetrate the skin will produce immunity As noted above, allergy or anaphylaxis or both almost always appear at the same time

Calmette⁻⁶ was much criticized in his immunological attempts with BCG because after a certain period his inoculated children and animals, which had previously been reactive, became refractive to tuberculin skin tests, that is, possessed no demonstrable allergy He was, however, able to show that in spite of this reprehensible deficiency, as it was called by those of the allergy-being-an-essential-part-of-immunity school, his animals were immune to reinfection There is still acrimonious discussion concerning the proof of the immunity in children MacKenzie¹⁸ in 1925 noticed that as he gave rabbits repeated intraperitoneal injections of heat-killed and later virulent pneumococci, his animals became anaphylactic and immune, but even with repeated injections they did not develop antibodies and there was no skin reactivity to the nucleoprotein of pneumococcus He found that the serum of these rabbits would when injected intravenously into normal rabbits protect the latter against many lethal doses of the pneumococcus, this protection was transferred without the accompaniment of allergy In a

later publication he reported some studies on the effects of repeated skin inoculations of pneumococcus nucleoprotein in rabbits. For about 10 to 14 days the animals became skin reactive but whether they were or were not allergic, their resistance to infection was no different from normals. Julianelle²¹ subsequently showed that continued skin activity could be obtained by and to the pneumococcus nucleoprotein but that there was no immunity.

This was indeed an important series of observations for it showed that in the anaphylactic, non-allergic animal there was immunity and further that allergy against pneumococcus proteins was not associated with immunity. Nevertheless, much remained to be done to prove the dissociation of allergy and immunity.

Willis has for years been in agreement with Krause in his belief in the protective nature of allergy. In 1928 he reported²⁷ that guinea pigs which had been infected two or three years previously with a strain of avirulent human tubercle bacilli (R_1) did not react allergically, as they had done previously, either to tuberculin or virulent H_{37} . They were, however, immune. He made no comment that this was, at least, an indication that allergy was not essential to immunity.

Among the first of the series of experiments noted above, Rich and Brown²⁵ in 1930 enlarged upon the investigations of MacKenzie. Rabbits were repeatedly injected by vein with large doses of heat-killed organisms, these animals became allergic and immune. It was possible passively to transfer this immunity to rabbits but it was not possible to demonstrate any transfer of allergy. In fact it is very difficult passively to transfer allergy to bacteria although it may be done with bacterial protein products. That same year Branch and Cuff²⁸ published their observation and among other conclusions stated that "allergy and anaphylaxis in tuberculosis are independent phenomena and immunity may be present without allergy."

In the next few years equally important studies were reported. Clawson²⁹ compared animals made allergic by repeated intracutaneous injections of heat-killed streptococci with those receiving the same dosage intravenously. The former became allergic, the latter did not. The allergic animals were slower in removing virulent intravenously injected organisms from the blood stream than the non-allergic. Furthermore, at the end of two hours there were more streptococci in the livers of the former group than in those of the latter. He felt that the allergic state did not in any way prevent the spread of disease and that the non-allergic animals had a better chance of recovery.

For a number of years, Florence Seibert³⁰ has been carrying out a succession of excellently conceived studies on the purification of the tuberculin protein and has finally obtained it in a very pure state. With it she has been able to disprove many of the old tenets on the relation of allergy to immunity, especially in tuberculosis. It was not through lack of trying that allergic responses were not obtained after repeated injections of old tuberculin into animals. It had been tried so often and so diligently that

"no tubercle, no allergy" was a common phrase. By repeated intracutaneous or intravenous injections of tuberculo-protein, in dosages in which the nitrogen content was equal to the amount of egg white nitrogen used in the routine sensitization of animals, she was able to establish in her animals a high grade of allergy which could be passively transferred. In addition to this she found that the allergic animals were not more resistant to inoculation with virulent tubercle bacilli than normals. Sabin and her co-workers³¹ corroborated this within a short time, more demonstrations that the allergic response per se is not a valuable protective mechanism.

As it was essential to show that animals which had been both immune and allergic would remain immune after the ability to respond allergically was removed, Rich and Jennings³² carried out a very ingenious and clear cut experiment. It is important to recall that those who insist that allergy is an integral portion of immunity, say that it is through the edema, inflammation and tissue destruction produced at the point of entrance of virulent organisms that the bacilli are halted and immobilized until they can be destroyed or ejected. Consequently, if it can be shown in an immune animal, in the absence of edema, inflammation and tissue destruction, that the injected virulent organisms remained grouped at the point of entrance one's belief in the necessity and benefit of allergic reactions would be at least shaken. Rich and Jennings were able to do this. Rabbits were made highly allergic and immune by repeated intracutaneous injections of heat-killed pneumococci. One-half of the animals were desensitized by the intravenous injection of a large dose of the same vaccine, they were thus rendered immune and non-allergic. These two groups as well as a group of controls received intradermally a virulent suspension of the same bacteria. That which was expected took place: the normal animals (controls) reacted with a typical inflammation which spread over a large skin area, the immune-allergic animals reacted with greater intensity than the controls and the lesions broke down with ulcer formation, the immune-non-allergic animals showed little if any reaction and recovered from the infection fully as well as the immune-allergic ones.

It is in the microscopic sections in this series of animals that a great deal of interest centers³³. In the controls there was a rapid spread of individual bacteria throughout the tissues. On the other hand in both the immune-allergic and immune-non-allergic groups, the organisms tended to remain in clumps as though agglutinated. Although the clumps slowly enlarged in diameter there was no distribution of individual organisms through the tissues. One is led to believe that the action of immune antibodies and not the altered tissue reaction (allergy) is the phenomenon which prevents the spread of organisms through the body.

The investigations of Rothschild, Friedenwald and Bernstein³⁴ add weight to the observation given above and have a more direct application to the human. They infected a large group of guinea pigs with an R₁ strain of tubercle bacilli: an organism which has been satisfactorily shown

to confer immunity When allergy was well established these investigators began to inject the test animals with minute but steadily increasing doses of tuberculin After a period it was possible to give them, without reaction, 10 mg of tuberculin, a dose of sufficient magnitude to kill the untreated infected animals This dose the normal controls tolerated without demonstrable damage At this time the three groups were infected intradermally with a virulent human tubercle bacillus, H_2 - The results were quite conclusive The local lesion in the untreated control appeared after some days as a small nodule In the untreated, but R_1 infected animal, a typical tuberculin reaction appeared, reached its full size in 48 hours, and healed after ulcer formation In the desensitized animals there appeared but a small nodule, no greater than that in the controls, but no evidence of specific tissue reactivity The control animals became riddled with tubercles, both the desensitized and the untreated R_1 infected animals possessed good immunity As the desensitizing injections were continued during the six weeks the animals were observed, there is strong evidence that continued lack of allergic response in no degree hindered the immunological process of the animals In fact, the desensitized animals suffered less for they did not sacrifice tissue through a sloughing ulcer as did the allergic ones

It has been mentioned above that the proponents of the belief that allergy is of essential importance state that the main protective service of the inflammatory reaction is to restrict the movement of bacteria and to prevent their dissemination Numerous investigators^{44 45 46, 47} have shown that although edema is the first change seen in the reacting allergic area, this is soon followed by an influx of polymorphonuclear leukocytes and later by monocytes It is their idea that the outpouring of leukocytes is important in forming a barrier to prevent the migration of the foreign material This subject has been clarified by Rich and McKee³⁰ as follows After animals were made immune and allergic, sufficient benzol was given them to remove most of their circulating leukocytes, then virulent pneumococci were injected intradermally into these animals and into a group of normal controls In the control animals the typical inflammatory reaction took place and the invading organisms were surrounded by leukocytes, in the test animals, there was no outpouring of leukocytes or fibrin but the bacteria became closely grouped and remained so Later the animals died as the immune antibodies could not dispose of the invaders without the aid of leukocytes

SUMMARY AND CONCLUSIONS

At this time the investigations bearing on the dissociation of allergy and immunity have abundantly demonstrated certain conditions

- 1 Animals which were once allergic and immune have with the passing of time become non-allergic but have remained immune

- 2 It has been possible actively to immunize an animal without the concomitant production of allergy

3 There is ample proof that although animals have become skin reactive to the bacterial proteins, they have not developed immunity

4 Animals which were allergic and immune have been desensitized without the loss of their immunity

5 It has been possible passively to transfer immunity to animals without making them allergic

6 By almost complete removal of the leukocytes from the blood stream of immune animals, it has been possible to show that these cells are not necessary to hold the specific antigen at the point of entrance

On this basis, one is justified in making the assertion that allergy and immunity are separate reactions and that the former is not necessary for the action of the latter. Because so little work has been done on man, one is not yet justified in categorically stating that it is always wise to remove allergy once it has been acquired, however, the results of the work on animals surely incline one to believe that this may be a good procedure. Equally important to consider is the possibility of actively immunizing individuals without making them hypersensitive.

There is, therefore, opened up a very sensible field for investigation which presents to the clinician the idea that he must seriously consider the establishment of some method of desensitizing the body without decreasing its immunity, tuberculin treatment in the human is an example of this. If the body can be prevented from reacting in an allergic manner, that is, with edema, inflammation and tissue destruction, the infected individual will be spared much discomfort in the course of his disease, and his convalescence may take place more quickly. It may well be that by this means a definite decrease in the mortality from infections will take place, a decrease in that mortality due to the allergic reaction which for years has been considered, without real basis, as an integral portion of immunity.

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EARLY RECOGNITION OF MYOCARDIAL DISEASE *

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THE diagnostic signs of myocardial disease may be grouped under two classes first those which are based on morphologic changes with obvious physical symptoms that make a direct appeal to the senses, and second those that are based on functional reactions, entirely subjective in character and often not susceptible to recognition by the human sense organs

In general practice two or possibly three distinct types of heart disease are encountered In childhood and young life the valvular affections prevail, usually the sequel of the acute infectious diseases, principally rheumatic and streptococcic infections which generally attack the valvular endocardium, but may involve the pericardium and myocardium Diphtheria, typhoid and the influenzal group of infections are further etiologic factors The resulting heart disease is recognized mainly by physical signs, subjective phenomena having a minor place in diagnosis

With middle life the effects of syphilis on the cardio-vascular system become more manifest Widening of the aorta area and accentuation of the second aortic tone are significant of the aortitis so common to this form of heart disease

The third type belongs to the aging period in the middle and later decades of life, often noted in the prime of life This form of heart disease is quite a different process, being largely the result of wear and tear with nutritive disturbances affecting principally the cardiac musculature and leading to degenerative changes with replacement fibrosis Its etiology is indefinite and often as obscure as the associated conditions of arteriosclerosis and hypertension Clinically it has no manifest or clear cut physical signs until the later or terminal stages of the process The subjective story is often very suggestive and diagnostic of the condition Distinctive and characteristic clinical pictures have been developed for the several advanced or terminal stages Acute coronary thrombosis is now recognized as a distinct clinical entity, and its prompt diagnosis is of common occurrence Chronic coronary artery disease or coronary sclerosis, likewise permits of ready diagnosis

The clinical evaluation of heart disease of all forms centers more and more around the question of the integrity of the myocardium Myocardial failure or insufficiency of varying degrees is associated with valvular disease and the different forms of chronic heart disease Its symptomatology is familiar and requires no repetition

The clinical onset in the chronic types is often of striking suddenness, occurring in individuals previously in apparently good health, yet in each

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condition it is safe to assume the existence of basic anatomic changes in the myocardium that have required a long period, probably years, to develop.

It is in this developmental period that the clinical syndrome of the early stage of myocardial impairment may be detected. Patients passing through this stage comprise rather a large group, they come to the attention particularly of the general practitioner and the dispensary or out-patient clinic, and are seen less frequently in a consulting practice.

It seems unfortunate in some respects that heart diseases have become a highly specialized field of medicine, and to a large extent have been taken out of general practice. Mackenzie¹ always contended that the general practitioner, by reason of his familiarity with the habits and history of the patient, was able to detect the earliest signs of disease.

The phenomena included in this syndrome or grouping of symptoms in early myocardial disease are almost entirely subjective, and perhaps have no definite sequence, yet considered concurrently they present a rather suggestive symptom complex. In a large measure these phenomena are expressive of a lowered myocardial reserve, and as such they have been considered by other observers.

The need of a careful history is evident, and its completeness will depend on the art and ability of the examiner to draw out of the patient the essential subjective complaints. The history should include a careful investigation of previous infections, particularly such as could produce damage of the myocardium, next, information as to the presence of a familial tendency toward diseases of the circulation is important, and, lastly, a definite history as to the various indiscretions of life which tend toward early vascular changes.

The leading symptom of this syndrome is fatigability. Clinicians are in accord that cardiac fatigue is one of the early signs of myocardial weakness. It represents a patient's reaction to effort, and is generally expressed as tiring or fatigue after the ordinary efforts or habits of his vocation and daily order of life.

The complaint is often of a tired feeling in the legs, more noticeable toward the end of the day. Frequently it is stated that he "is not as good as he used to be." Often there is added the element of fear, or disinclination to perform the usual tasks.

Fatigue is a sensation known to everyone and the term is often loosely applied. It may not be realized that its signs and symptoms affect every body tissue—glands, sense organs, and central nervous system, being just as susceptible as the muscles.

As Wiggers,² the physiologist, has aptly stated, functional reactions in disease differ from those in health only in degree, and there are no pathologic processes in disease capable of evolving new types of functional reactions. The physiologic conception is that manifestations of fatigue are direct criteria of an oxygen debt and of the accumulation of lactic acid. The more rapid development of fatigue in heart disease merely signifies a

deficiency on the part of the cardio-respiratory system in meeting the increased demands of muscles during exercise

Expressed in another way, the physiologic ability to respond to exercise without fatigue becomes a direct measure of the compensatory mechanism held in reserve by the heart, that is, the myocardial reserve

The inability of the diseased heart to compensate for this circulatory inefficiency is due to loss of the myocardial reserve. Again it may be said that in heart disease the oxygen debt is incurred with a less amount of work, and lactic acid accumulates more rapidly

It may be assumed that with early changes in the coronary circulation the inefficiency of the heart muscle will be manifested by cardiac fatigue

Circulatory fatigue may show itself in the form of insomnia, which can be grouped among the early signs of lowered myocardial reserve

The mimicry of gastric symptoms in advanced coronary disease is well known, and it is logical that to a lesser degree this occurs in connection with myocardial weakness. These are expressed under the guise of loss of appetite, gaseous distention and a feeling of pressure in the upper part of the abdomen, the chemical and roentgenologic manifestations being negative. Riesman³ has aptly referred to them as gastric masquerades, adding that apparent disease in the upper abdomen often has its seat of origin in the heart

Certain vasomotor disturbances are a definite part of this syndrome, such as vertigo, giddiness, syncope and occasionally convulsions. Again such psychic phenomena are noted as mental haziness, impaired memory, stupor, drowsiness and hallucinations of sight, hearing and smell. It seems well determined that aside from primary disorders of the nervous system or chemical alterations of the blood, cardio-vascular disorders are frequently responsible for the symptoms of dizziness, unconsciousness, and the psychic phenomena previously referred to. The cells of the cerebral cortex are extremely sensitive to any marked diminution of its supply of oxygenated blood even though temporary, and react promptly by the manifestations as stated. These occur often with simple postural changes, as lacing a shoe, bending forward suddenly, or other movements incident to the occupation of the individual

Recent investigations have shown that the metabolism of the brain does not differ greatly from that of other tissues. The rate of lactic acid formation in the brain tissue appears to be higher than that of the body as a whole, and the normal blood flow per gram of brain substance is larger than that for skeletal muscle, heart, liver or spleen. It is not surprising, therefore, that cerebral activity should be seriously affected in conditions of reduced myocardial reserve as well as in advanced stages of decompensation. These somewhat vague phenomena may accompany or usher in that triad of symptoms which Kauffman⁴ has termed the three steps to heart failure: (a) breathlessness, (b) palpitation and (c) substernal discomfort.

Breathlessness is probably the most important feature of this syndrome, but it again requires a fine distinction to determine whether this is a normal physiologic response or a pathologic manifestation. It is important to determine whether the change in functional response to certain effort tests such as climbing stairs, walking up a slight incline, and daily routine duties are phenomena that have not been noticed before. Often the time taken to return to the resting state will be longer and sometimes painful.

Long before the stage of circulatory failure is reached, the patient with heart disease differs apparently from normal persons only in the degree of muscular activity that brings on dyspnea and weakness.

The normal individual is ordinarily not conscious of the vigorous normal movements of the heart, because he has become accustomed to them. The sign of *heart consciousness*, as manifested by flutter, skipping beats, thumping and palpitations, occurring in middle life after a meal or physical effort, should therefore be given careful evaluation. It is specially significant if such symptoms have not been noted previously. When associated with breathlessness and fatigue, heart consciousness becomes an important part of the total syndrome.

The sensation of *substernal discomfort* is the one symptom that most frequently causes the patient to seek medical advice. Like the expression "heart consciousness," it is a sensation that is difficult for the average patient to describe. Some express it better than others. The sensations apparently may extend from a mere feeling of heaviness over the upper part of the chest to the terrible vice-like constriction experienced in certain forms of angina pectoris. Herrick⁵ has referred to the lesser forms of substernal discomfort as a mild type of angina. That it is invariably associated with physical effort still further confirms this relationship.

Substernal discomfort or distress, unlike breathlessness and palpitation, is rarely masked under any other guise. It is localized more frequently to the left than to the right of the upper part of the chest and radiation is uncommon.

While the subjective phenomena constitute the essential part of this syndrome, certain physical or objective signs have an important relation to it. Of these a demonstrable enlargement of the heart has assumed a primal importance in the recognition of early myocardial disease. Christian,⁶ Stroud,⁷ Eyster⁸ and others have given special significance to this symptom. Eyster considers that the differentiation of the enlarged heart from the heart of normal size is the most important single factor in determining the presence or absence of organic heart disease.

The greatly hypertrophied heart in advanced organic disease is easily recognized by the usual methods of physical examination, but there is need for more accurate differentiation of the hearts that are less abnormal and associated with an earlier stage in the pathologic process.

Studies in most of the lower animals have shown that the weight of

the heart is more closely related to the size of the body than is the weight of any other organ with the exception, perhaps, of the brain

An estimation of the cardiac size in man can be made only indirectly by the projection of one or more of the surface planes of the heart. Of the two general methods employed for this purpose topographic percussion, and the roentgen-ray projection, the latter is now considered more objective and accurate

In a series of contributions from 1924 to 1928, Hodges⁹ and Eyster¹⁰ established tables predicting cardiac area and cardiac transverse diameter in the frontal plane from height, weight and age, as criteria for determining the presence or absence of cardiac enlargement. These were adopted in 1931 by the Heart Committee of the New York Tuberculosis and Health Association and are now recommended by the medical departments of many life insurance companies. These tables are now generally regarded as the most accurate standard available, when used with postero-anterior roentgen-ray plates, and this method is considered superior to the use of the cardio-thoracic ratio

While the tendency is to a most complete use of the roentgen-ray in examination of the gastrointestinal tract, it receives much less consideration in cardiac disease, although it is of equal importance. By means of the fluoroscope, orthodiascope, teleroentgenogram and signs of either right or left ventricular preponderance in the electrocardiogram, definite evidence is presented of the degree of cardiac enlargement

The truest estimate of encroachment on myocardial reserve is therefore best arrived at by the determination of cardiac enlargement. The presence of cardiac enlargement is always of potential significance, it may be the earliest physical sign of myocardial impairment. Of minor import are blood pressure changes as the result of physical exertion. These have been variously interpreted. No satisfactory exercise test has yet been devised. An elevation of 20 mm of mercury after one of the customary exercise tests is regarded as a sign of myocardial weakness. A change in the pulse rate after exertion is also regarded as having some diagnostic significance. When the pulse rate requires longer than five minutes to return to the resting figure, it suggests an impairment of myocardial reserve

VENOUS PRESSURE

Recent observations on venous pressure and its more extensive use in clinical examinations suggest that it has a significant relation to the dynamics of the failing heart. Eyster¹¹ reaches the conclusion that venous pressure is clinically an index of cardiac function and that its clinical significance is largely confined to the one condition of impending or present cardiac incompetence. Venous pressure in cardiac insufficiency varies from the upper normal level (100–110 mm) to 300 mm of water or more. The extent of the failure is roughly proportional to the rise, and the clinical

progress of the patient and the prognosis of the condition are largely revealed by the trend of venous pressure. Frequently a change in venous pressure precedes other clinical signs. Cardiac incompetence has been described as that condition in which the venous pressure exceeds the range within which the heart is capable of responding by increased work to an increased venous load.

ELECTROCARDIOGRAPHY

The electrocardiogram in the early stage of myocardial disease has thus far not been regarded as of especial significance. Signs of conduction disturbance and changes in the ventricular complex are most apt to be found. Left axis deviation occurs so frequently in middle and advanced age periods that many observers regard such a sign as normal, yet, on the other hand, interesting studies have been reported by Luten and Grove,¹² and more recently by Hyman and Parsonnet,¹³ that are very suggestive. In observing the development of bundle branch block from the beginning, they noted that the cases showing early left axial deviation with altered T-waves in the first lead later developed into full blown bundle branch block. As more frequent and serial electrocardiographic studies are made, particularly as additional leads will clear up the so-called silent areas, it is reasonable to expect that early changes will be noted that will prove of diagnostic value.

The nosology or description of the diseases of the heart has varied and kept pace with the changing conceptions of the underlying physiologic and pathologic processes.

Various clinical terms have been proposed for the degenerative type of cardiac disease. While chronic myocarditis has been the usual designation, it is not very expressive nor properly related to the existing disease condition.

Christian¹⁴ has proposed the term chronic non-valvular heart disease, yet admitting that it was not entirely satisfactory.

For the syndrome or group of phenomena, subjective and objective, encompassed in the early stages of myocardial impairment, the term myocardosis has been suggested, being first proposed by Riesman¹⁵ in 1926. Hyman and Parsonnet¹⁶ have published several comprehensive articles under this title. It is a generic term signifying myocardial disease and in that sense rather expressive of the condition. Considered separately, each phenomenon occurring in myocardosis is not diagnostic, but taken concurrently they form a clinical picture that permits of ready recognition. The term is mainly expressive of the myocardial reserve of the heart, which is an important factor in the complicated mechanism of the circulation, and it is likewise suggestive of early anatomic changes in the myocardium. The field of early myocardial disease is open for fruitful investigation, and it offers alluring prospects in the study of the various phases and stages of coronary disease now beyond our ken.

The early recognition of myocardial disease entails a considerable responsibility on the attending physician. The public has a greater fear of

heart disease than of any other disease, except cancer or perhaps syphilis. As Herrick¹⁷ has said, it is easy to sow the seed of fear of heart disease. Phobias may be started and neurotic individuals made more neurotic with a consequent lessening of their activities and happiness. Yet the fullest cooperation of the patient is needed if during the early stages any attempt is to be made to curb or combat the relentless progression of the vascular degenerative changes in the heart peculiar to the middle and later decades of life. It is of primal importance that the patient accept the view that the aging process is a physiologic change and does not permit the same activities as in younger years. When the condition clearly indicates an encroachment on the normal myocardial reserve, rest and limitation of activities should be the main essential in outlining a proper regimen of living.

The proper appreciation of the syndrome of early myocardial disease offers the one hope of modifying and possibly controlling the tendency to progressive and more serious myocardial damage, and, above all, it opens up a new field in preventive medicine that is worthy of our best efforts.

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STUDIES OF CELL POTENCIES AND SOME RELATIONS TO NEOPLASIA *

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THERE is a timed sequence of three fundamentals concerned in any increase in cell number in multicellular organisms, and these are the processes of proliferation, differentiation and organization. Since they are dynamic processes which proceed in regular but overlapping order at any given stage of growth and development, it is exceedingly difficult to experiment with them in the higher animals, including man. Both observation and experiment are easier in lower animals, and because they are so fundamental and occur in all types of living things, it is justified to study them in any organisms in which the experimental conditions can be simplified. Especially important is it that their dynamics be studied, that each be segregated from the others, that one or the other be interrupted separately at various points, that the time relations be manipulated, and so on.

To make the terms themselves clear, definitions of them can be given as follows. Proliferation is simply the multiplication of cells. Differentiation is the changes in the cells which lead from the more general to the more specific, or at another stage of the process differentiation is the result of that series of changes occurring within the protoplasm of cells which bring them to the point of being able to perform their functions as members of an adult organism. Organization may be defined as the harmonious, co-operative development of cells of various differentiations so that they can function in the frame of a whole organism.

Proliferation is a function common to protoplasm in whatever living thing it is found. Differentiation and organization, on the other hand, lead to the development of the anatomic and functional peculiarities of each individual, species, genus and family. They are, in other words, the processes which lead to the production of a human from a human fertilized ovum, a dog from a dog fertilized ovum, and so on. Obviously, the factors which determine differentiation and organization are contained within cells and come from parents. We might stress further the point that of the two, organization is the more specific, for differentiations in similar directions occur in many unlike organisms as, for instance, both giraffes and humans have epithelial cells, whereas strict specificity, that is, the way epithelial cells and others are arranged, is what determines that a human is built upon human plans.

Another obvious point in the relations between the three processes is that when differentiation and especially organization have occurred to the extent of producing an example of the proper species, proliferation ceases.

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Therefore differentiation, and especially organization, are natural inhibitors of proliferation. Still another relation is obvious when we put it in this form: cells cannot differentiate and organize unless they are present. Therefore proliferation is a necessary preliminary to the others. An important deduction is, that if differentiation and organization do not occur, cells continue to proliferate, e.g., in tissue cultures. Also when organization is disturbed as by an injury, proliferation begins to repair the injury and continues until organization again puts a stop to it.

Now the relation to neoplasia can be put in some such wise: the cells of all tumors proliferate, else, of course, they would not grow. The cells of many tumors differentiate, sometimes fairly perfectly, but the cells of no tumors organize normally. Since, therefore, the factors governing differentiation and organization are present within the cells and since tumors often grow in the very same environment in which normal cells are differentiating and organizing, it would seem that the cause of tumors lies in a failure of their differentiating and especially their organizing powers, or potencies, to introduce this term. Shall we say, then, that the cause of the continued growth of tumors is the failure of their cells to differentiate, and especially organize, properly?

The experiments to be described were directed toward the proliferative phase of cell growth and development. This is an extension of the use of the new tool—sulfhydryl. The story of F. S. Hammett's discovery of this sulfhydryl group as a normal, essential chemical stimulus to cell division and his demonstration that partially oxidized derivatives of this group inhibit cell division has been told before. Suffice it to say, that up to the present, cell division in some 40 odd species of animals and plants, including man, has been found responsive. Results obtained with this reduced-partially oxidized sulfur equilibrium can be translated directly in terms of the normal, something which could not be done until it was discovered, and cannot be done when extraneous cell-division stimuli are used such as tar, roentgen-rays, scarlet red and many others.

The experimental material which I will now show consists of the skins of rats, mice and guinea pigs, and the regenerating claws of hermit crabs. Both were subjected to sulfhydryl, the one to simple application to their skins, the other to living in sea water to which sulfhydryl was added. In addition the crabs were subjected to partially-oxidized sulfur, the inhibitor.

The skins of rats, mice and guinea pigs are simpler than those of humans and consist of a few layers of epithelial cells with no regular arrangement of basal layers, spinous cell layers, pigmented layers. A few groups of cells in the middle layers show spinous structure, a few pigmented cells are found and a few are oriented vertically in the basal layers. After application of the sulfhydryl group, the picture changes amazingly. The cells in the basal layer are practically all oriented vertically as a result of their increased mitotic activity, a definite basement membrane appears. A full and complete layer of spinous cells appears, and a layer of pigmented cells

The increased number of epithelial cells comes from the younger, incompletely differentiated cells of the skin. Adult, fully differentiated epithelial cells of the skin are incapable of division.

In all probability, this latter statement can be expanded to the point of declaring that when any cell is completely differentiated it can no longer multiply. Needless to say, this is extraordinarily difficult to prove, if for no other reason than that accurate methods of quantitative measurements of degrees of differentiation of cells are still to be worked out. Among other implications of this statement, however, are these: wherever continuous or interrupted cell multiplication occurs there must be present "spare parts," so to speak, from which the multiplication can begin, and cells in any given organ or part which retain the power of multiplication for whatever reason, physiological increase in number, repair, regeneration, etc., are not fully differentiated. Which, in turn, means that evolution has not ceased. But will anyone say it has?

At any rate this is a specific reason for the previous statement that differentiation and organization are natural inhibitors of proliferation.

To return to the mouse skins, I repeat from Hammett's interpretation of the biological significance of the picture: the stimulation to rapid division results secondarily in an expansion in the rate and degree of the differentiating and organizing potencies of the cells.

If, then, experimental increase in the rate of cell division obtained with a natural stimulus—sulfhydryl—results not in diminished, but in increased differentiation and organization of the cells so stimulated, it follows that increased rate of cell division alone can never lead to malignancy. Something must happen to their differentiating and especially organizing potencies. Incidentally this is why sulfhydryl alone should not produce malignancy.

Suppose the rate of cell division which is normal to any given growth and developmental process be retarded. Hammett has shown with partially-oxidized sulfur groups in a variety of material what happens then. Conversely, when the rate of cell division is retarded, so also are the degrees of differentiation and organization. But at any given time period, comparison of the retarded material with that of the controls shows that the retarded material is identical with the controls of an earlier time. Therefore decreased rate of cell division alone does not lead to malignancy. I use diagrams (published elsewhere) of regenerating hermit crab claws under the influence of sulfhydryl, sulfoxide, and the appropriate controls to illustrate these points.

In 269 regenerating claws which were studied, 44 growth aberrations were found. A study of them by serial section and comparison with the normals allows an answer to another question.

It is obvious that the sequence under discussion, viz., proliferation, differentiation and organization, must be timed properly or an abnormal part will be produced. Will this abnormal part be a neoplasm, or will it,

in the end, organize as best it can, bring proliferation to a stop, and result in merely a growth anomaly? The answer as written in the crab claws is as follows

In some of the claws, breaks in the chitinous envelope, being laid down as the new claw regenerated, opened this barrier to the proliferating cells. They streamed through and produced an unorganized mass. Since sulfhydryl is a specific stimulus to proliferation, all those claws with defects which were exposed to this chemical group developed growths, and all of them were much larger than those which appeared in the controls (75 per cent), or in the retarded, i.e., sulfoxide-treated, specimens (43 per cent). In other claws unorganized growths were found at the tips of the distal segment of the claw. Study of serial sections and of timed specimens showed that differentiation and organization were progressing in addition to the proliferation, but that the timing of these processes was thrown out of gear. There is no doubt that the growths would eventually have ceased proliferating and smoothed out to a bump on the claws.

Several other specimens of special interest were found, such as a hyperchitinous corresponding to hyperkeratosis, and a second regenerate attempting to grow within the stump. In all of these the same phenomena occurred, viz., the potencies of differentiation and organization within the cells attempted expression, even though the time relations were disturbed and the environment was changed. Important to the present consideration is the fact that proliferation was inhibited.

Space forbids further discussion, even though but a very few of the fundamentals involved in these experiments have been touched upon, really they have only been mentioned. One of the many practical applications may be hastily sketched, however. The time factor is often the crux of the situation in the ordinary pathological diagnosis of tissue. In the edges of gastric ulcers, epithelium is often found in the midst of granulation tissue and the question arises. Is this repair or carcinoma? What would have happened if the surgeon had not removed the ulcer when he did? If merely the relative rates of proliferation, differentiation and organization have been shifted, it is not carcinoma. Nor is it carcinoma if the cells ensnared in a different environment are attempting to express the normal potencies of differentiation and organization within them. That much discussed, but quite impractical subject of tumor grading also is more than touched by these considerations.

What then is the distinguishing feature of malignancy? Increasing the rate of cell division does not change these potencies, in fact it allows of more full expression. Decreasing the rate does not cause neoplasia. Facts from which we cannot escape are that the cells of neoplasms differentiate imperfectly and do not organize, even when in the very same environment in which normal cells are accomplishing these processes. Nor is it a fault in timing as even the inexperienced in oncology can testify, and as the experiments discussed above show. Since the potencies of differentiation

and organization are contained within the cells, the fundamental cause of neoplasia must be a change within them

That there are degrees to this change is also evidenced by numerous facts. The better the differentiation of the cells of a tumor, the slower its growth as tumor grading in its statistical application has shown. But this is but in harmony with the biological truism that the less mature an embryo, the more rapid its growth. In other words, malignancy and benignancy of a neoplasm, in the sense of its rate of proliferation, its invasive properties, its autonomy, etc., can be directly correlated with its deviation from the appearance of the structure which normal cells would produce under the same circumstances.

I, as well as others, have been dissatisfied with even the definition of what a neoplasm is, let alone with many of the views on the subject. In summing up, as good a way as any is to do it in the form of a definition. For the time being, and until and unless more knowledge demands its revision, we say that a neoplasm is a mass of cells which arises from and continues to proliferate within an organism as a result of and in direct proportion to their degree of internal qualitative differences from the other cells of the organism with respect to the potencies of differentiation and organization particularly.

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Full descriptions of the experiments and full discussion of their significance, of which this paper is a partial summary, together with pertinent literature, may be found in

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EDITORIAL

THE SO-CALLED 'CIRCULATORY HORMONES'

IN the past few years the rôle of the so-called "circulatory hormones" has been an interesting and ever changing one. The first circulatory hormone was described in 1926 by Frey and Kraut¹. They isolated a substance from urine which, on intravenous injection into dogs, caused a fall in the blood pressure (in the systolic more than in the diastolic) and an increase in the amplitude of the heart contractions. This substance was called "kallikrein," later "padutin." They observed the same active substance in the blood except that it occurred in an inactivated form and had to be especially treated to produce the reactions. After the active substance had been found in the blood, they tested, by intravenous injection, fresh extracts of liver, kidney, and spleen and obtained results similar to those which had occurred with extracts of urine and blood.

In 1929 Frey observed that the fluid evacuated from a large pancreatic cyst contained an enormous amount of the active substance. On further investigation on animals he found that, after total extirpation of the pancreas, the amount of active substance in the urine decreased as much as 80 per cent. He concluded from his experiments that the pancreas was the site of formation of the active substance, that it was stored in various other organs and tissues, and that it was excreted in the urine. Extracts of pancreatic tissue were found to contain considerable amounts of the active substance. Frey used the urine extract kallikrein, or padutin, for his clinical work, however, and injected it intramuscularly rather than intravenously. The physiologic action was believed to produce vasodilatation and, when injected in the rabbit, dilation of capillaries in the ear was observed. Frey felt that this action was not due to the presence of histamine and choline.

Gley and Kisthonos,² in 1929, working in France, prepared an insulin-free pancreatic-tissue extract which they injected intravenously into rabbits. They found that it produced a transitory fall in blood pressure, had vasodilator properties, antagonized the action of epinephrine, and that these effects were not due to choline, histamine, or peptones. This extract may be identical with the circulatory hormone of Frey and Kraut. Standardization of the extract was on the basis of hypotensive units per cubic centimeter. A unit was considered to be the amount of extract necessary to produce barely perceptible evidence of a drop in blood pressure on the tracing when the substance was injected into the jugular vein of a rabbit weighing 2 kg. Wolff, Findlay, and Dessin³ prepared a pancreatic tissue extract after the

¹ FREY, E. K., and KRAUT, H. Über einen von der Niere ausgeschiedenen, die Hertz-tätigkeit anregenden Stoff. *Ztschr. f. phys. Chem.*, 1926, clix, 32-61.

² GLEY, P., and KISTHONOS, N. Recherches sur la substance hypotensive du pancreas, *Presse med.* 1929, ii, 1279-1282.

³ WOLFF, I. B., FINDLAY, D., and DESSIN, E. Treatment of angina pectoris with a tissue vasodilator extract, preliminary report. *ANN. INT. MED.*, 1931, v, 625-642.

method of Gley and Kisthonos, and they corroborated the latter's findings inasmuch as they found that it caused a primary drop in arterial blood pressure when injected intravenously, slowed the heart rate, and antagonized the action of epinephrine.

After intramuscular injection both the padutin of Frey and Kraut and the pancreatic tissue extract were found to give favorable results, particularly in the treatment of cases of angina pectoris. Frey further noted improvement in cases of essential hypertension and in vascular disease, especially in cases in which intermittent claudication was present. He attributed the beneficial results to the vasodilator effects of the extract. Wolff, Findlay, and Dessin used the pancreatic tissue extract among patients with angina pectoris and reported clinical relief in 55 per cent of cases.

Subsequently, Wolff, in collaboration with the Sharpe and Dohme laboratories, made a new, standard, pancreatic tissue extract in which 1 unit would neutralize the pressor effect on anesthetized dogs of 0.001 mg. of epinephrine. His change in the standardization followed the work of Levine, Ernstine, and Jacobson, in which they demonstrated that, by subcutaneous injection of patients suffering from angina pectoris with 1 cc. of a 1:1000 solution of epinephrine, an anginal attack could be induced, whereas no such attack could be produced among normal control subjects. Wolff reasoned that, if epinephrine injected into certain patients subject to angina pectoris would produce an attack, and if a certain vasodilator obtained from the pancreas moderated the action, the favorable results obtained in treatment might be explained by the ability of the tissue extract to neutralize epinephrine. No further standardization of the pancreatic tissue extract has been made.

Up to this time the development of circulatory hormones had been concerned with lowering of the blood pressure, vasodilator properties, and neutralizing the effects of epinephrine. In 1930 J. S. Schwartzmann⁴ prepared an extract from skeletal muscle. He assumed that some sort of antispastic substance was at work during the contraction of active, skeletal muscle. The fact was known that anginal pain sometimes disappeared if the patient continued his muscular effort. This extract was called "myoston" and it was standardized on the basis of its adenosin phosphoric acid content, each cubic centimeter containing 2.5 mg. This standardization was interesting in view of the previous work of Drury and Szent-Gyorgi, who studied the effect on the mammalian heart of extracts of heart muscle, brain, kidney, and spleen, and who found a definite and transient effect on the heart. They isolated the substance which they felt was responsible for the reactions, and from its chemical properties they believed it to be adenylic acid or adenosin phosphoric acid. They found also, that adenosin prepared from yeast nucleic acid had an action identical with that of adenylic acid. They intravenously injected into animals both the tissue

⁴ SCHWARTZMANN, J. S. Muscle extract in the treatment of angina pectoris and intermittent claudication, *Brit. Med. J.*, 1930, 1, 855-856.

adenylic acid and the adenosin, and they observed a lowering of the blood pressure which they thought was due to the slowing of the heart rate and to general arterial dilatation

In contrast to these observations Nuzum and Elliott reported that, following intravenous injection of guinea pigs with pancreatic tissue or the Frey "hormone," these substances did not cause a transitory, complete heart block, a supposedly specific test for adenylic acid and adenosin Wolff, however, noted that 250 micromilligrams of adenosin phosphoric acid corresponded in activity to 1 cc of pancreatic tissue extract It is still impossible to say what the common active substance is

Myoston, on intramuscular injection, gave excellent results in cases of angina pectoris, as reported by J S Schwartzmann, and M S Schwartzmann treated a few patients with intermittent claudication very successfully Myoston has also been prepared for oral administration, but its effect is more transient and, at present, adequate dosage would be almost prohibitive in price

More recently, excellent results have been reported by clinicians of The Mayo Clinic⁶ with the use of pancreatic tissue extract, myoston, muscle adenosin phosphoric acid and adenosin, administered intramuscularly to patients with occlusive disease of the peripheral arteries in whom claudication was the major complaint To evaluate these extracts more accurately, these workers described a standard test for quantitating claudication Injections of known vasodilating agents were made before the extracts were administered without effecting a significant change in tolerance to exercise Following intramuscular administration of the extracts, a sharp increase in the amount of exercise was possible, which persisted for days

Up to this time the beneficial results have been attributed by various workers to the vasodilator action, but later workers have shown that the improvement bore no relationship to dilation, as measured by standard methods Pancreatic extract and myoston do not cause a rise in skin temperature or an increase in the rate of heat elimination from a limb It was thought that the action was probably a direct one on the muscle, supplying a deficient substance or neutralizing an accumulated metabolite in the presence of anoxemia of the muscle Dietrich and Schwiegk have shown that in animals coronary flow is increased by these extracts Their use in coronary disease may prove beneficial and they may thus in the future have a wide clinical application

G R

⁶ BARKER, N W, BROWN, G E, and ROTH, G M Effect of pancreatic tissue extract on muscle pain of ischemic origin (intermittent claudication), Trans Am Therap Soc 1933 LXIII 115-119

⁷ ROTH, G M and BARKER, N W Observations on the use of skeletal muscle extract in treatment of intermittent claudication, Proc Staff Meet Mayo Clinic, 1934, 18, 390-392

REVIEWS

Diseases Peculiar to Civilized Man By GEORGE CRILL, M D xi + 427 pages, 15 x 32 cm The Macmillan Company, New York 1931 Price, \$5 00

This book is an exposition of the theory of its author that hyperthyroidism, neuro-circulatory asthenia, peptic ulcer, and possibly other diseases, are due primarily to the stress and strain of civilization. He calls them "kinetic diseases," and believes them due to an abnormally high sustained activity of the adrenal-sympathetic-thyroid system, or of some of its component parts. Several persons have contributed sections on specialized topics. A section of the book is devoted to a description of certain surgical methods, particularly denervation of the adrenal, and operative procedures upon the sympathetic. Over one-half of the book is given over to detailed case histories. There is a fair bibliography.

This work gives a very readable account of an interesting and superficially plausible theory. The claims made as to the beneficial effects of adrenal denervation are certainly broad. An effort is made to include diabetes in the list of kinetic disorders, and the author makes the flat statement (page 155) that "in a small group of cases, adrenal denervation has abated or cured diabetes." He also believes that the same procedure "abates or cures peptic ulcer." He seems to have established, to his own satisfaction, that bilateral denervation of the adrenals does not cause chronic adrenal insufficiency in man. As he states, the recuperative power of the adrenals is very great.

The accounts of the cases of acute adrenal insufficiency following denervation are of great interest, especially Case 1, page 124. It seems probable that this constitutes an instance of the true experimental production of Addison's disease. Following bilateral denervation of the adrenals, the patient ran a six weeks' course with asthenia, increasing pigmentation, hypotension, and increased concentration of blood non-protein nitrogen (urea). Autopsy indicated degeneration of both adrenals, which was considered secondary to thrombosis and obliteration of the blood vessels.

It seems unnecessary to dwell, in view of the present state of our knowledge, upon the potential dangers which certainly attend any surgical interference with the adrenal glands, and in hands lacking the technical skill of the author of this book, such dangers will doubtless be very much increased.

G H

A Textbook of Medicine By 141 American authors, Edited by RUSSELL L. CECIL, A B, M D, Sc D, and FOSTER KENNEDY, M D, FRSE. Third Edition. xi + 1664 pages, 18 x 25 cm. W B Saunders Company, Philadelphia 1933. Price, \$9 00.

In his preface to this work, the Editor states "In order that physicians and students might have the benefit of an authoritative and up-to-date treatise on every medical subject, it seemed desirable to prepare a textbook of medicine in which each disease, or group of diseases, would be discussed by a writer particularly interested in that subject. This book represents an effort to carry out such a plan." The appearance of the third edition, six years after the first, indicates that the plan has been very successful, and examination of the book reveals the causes of its popularity.

One hundred and thirty well known writers have contributed articles. Though one feels at times that there may have been too much division of labor, the description

of different phases of a subject by various writers is usually managed with coherence in plan and similarity in style of presentation. Thus the section on tuberculosis is divided into seven parts and contributed by five authors. Uniformity in style and quality of their work, however, makes this section a very well organized unit. Certainly in the section on diseases of the kidney, the articles on anomalies of urinary secretion, uremia, and nephritis, would be much better correlated if they were contributed by one author instead of by three, as differences in terminology used may be somewhat confusing to students. This difficulty has been partially obviated by including, in the article on nephritis, Christian's recently published table indicating the terminology of no less than ten different classifications of Bright's disease in common use. This should help the student to a better understanding of this frequently confusing subject.

Any attempt to list even a few of the contributors would be useless, as it would simply consist in calling the roll of many of the most prominent American teachers, all of whom are eminently qualified to discuss the presented subjects.

Generally, the minor criticisms that might be offered are greatly outweighed by the evident good qualities of the book. The articles are uniformly well written, clear, interesting, up-to-date, and with few exceptions, unusually well correlated.

The size and broad scope of the volume make it impossible to review any more detailed account of its contents. Certainly, it may be recommended to students as a modern and complete textbook.

T N C

Clio Medica: Medicine in Persia. By CYRIL ELGOOD, M.D. 105 pages, 11 x 17 cm.
Paul B. Hoeber, Inc., New York City. 1934. Price, \$1.50.

By this time this series of handy little volumes on medical history ought to be pretty well known to the profession. Everyone interested in medicine in any of its aspects should own these books which can be put in the pocket and read while waiting for any reason, and it is an unusual doctor who does not have spare minutes which are usually wasted. The author of this latest addition was at one time physician to the British Legation in Teheran and had ample time to study the history of one of the most interesting countries on the globe. The land of Scheherezade and Omar Khayyam, of Rhazes and Avicenna, Ismail and Haly Abbas, where 'Jamshid gloried and drank deep,' has a fascinating history beginning indeed with that legendary hero, for as Firdausi puts it:

Jamshid thus spent
Another fifty years and did much good
He introduced the scents that men enjoy,
As camphor, genuine musk, gum Benjamin,
Sweet aloe, ambergris, and bright rose-water
Next leechcraft and the healing of the sick,
The means of health, the cause of maladies,
Were secrets opened by Jamshid.

Health and disease in early Persia were gifts of the gods and thus it seems that the inhabitants did not let it go entirely at that for in the there is the record of an early section the use of an Elgood quotes as follows:

His birth
So wilieth
A blue-steel
Because the

Her pain and fear, then let him ply his craft
 And take the lion from its lair by piercing
 Her waist while all unconscious Then imbruing
 Her side in blood, stitch up the gash
 Put trouble, fear, and care aside, and bruise
 With milk and musk a herb that I will show thee,
 And dry them in the shade Dress and anoint
 Rudaba's wound, and watch her come to life

When Alexander the Great (whose medical history has recently been written by an Italian) went to Persia, Firdausi relates, that an Indian rajah gave him four gifts a girl, a philosopher, a magic cup and a physician

A youthful leech who diagnoseth
 Disease by making an uroscopy,
 So long as he is at the court, the Shah
 Will never ail

We go through the Seleucid and Sassanid ages, the Caliphate and Baghdad school, with Rhazes and Avicenna and Ismail, the great medical trinity of the day, if we may speak of a couple of centuries as a day The later history is not so brilliant, the Caliphate decayed and the Mongol and Safavid dynasties ruled, then the Qajar dynasty lasted until 1926, when Reza Khan became ruler starting the Pahlevi dynasty A fascinating story condensed in scarcely more than a hundred pages

J R

L'Exploration Clinique Medicale-Technique et Semeiologie Published under the direction of ÉMILL SERGENT, Professor of the Faculty of Medicine of Paris Sections by him and nine collaborators Paper, two volumes, 1165 pages Masson and Company, Paris 1934 Price, 120 francs

In 1913 Sergent published the first edition of his *Traite Élémentaire d'Exploration Clinique Medicale* Five editions followed quickly, with translations into Italian, Spanish and Roumanian The treatise was both a guide to the student and a stimulus to the teacher Now after a lapse of years Sergent brings up to date the newer knowledge of the technic of medical examination and the signs of disease

The two volumes comprise sections on The Respiratory Apparatus, by Émile Sergent, The Circulatory Apparatus, by Camille Lian, The Nervous System, by Paul George, The Sympathetic Nervous System, by René Mignot, Radioscopie and Radiography of the Thorax, by Pierre Pruvost, Radiography of the Nervous System, by Pruvost, Examination of the Abdomen, by R d'Heucqueville, Examination of the Digestive Tract, by d'Heucqueville, Laboratory Methods Applicable to Diseases of the Digestive Tract, by Pierre Oury, Examination of the Spleen, by d'Heucqueville, The Liver and Hepatic Function, by Ribadeau-Dumas, The Pancreas, by Bordet, Kidneys and Urinary Function, by Ribadeau-Dumas, Analysis of Urine, by René Hazard, Examination of the Blood, by Pruvost and Bordet, Elementary Laboratory Methods, by Pruvost, Radiology of the Abdomen, Extremities and Vertebral Column, by Pruvost

The volumes are well printed, with numerous excellent plates and illustrations There is a good index This new edition of a very popular earlier work will no doubt serve the same useful purpose as its predecessor and will meet with approval It has been edited with much care and gives due credit to work done outside of France

W B S

The Science of Radiology Edited by ORTO GLASSER, Ph D, of the Cleveland Clinic Foundation 311 + 450 pages, 17 5 x 25 cm Charles C Thomas Springfield 1933 Price, \$4 50

This is a much needed and timely book, sponsored by the First American Congress of Radiology The editor, Otto Glasser, is well qualified by virtue of his extensive experience in Europe and America in the physics of radiology, and also through his close contact with its clinical applications The contributors are all outstanding men, occupying high positions as physicists or clinicians

The book depicts "the outstanding features developed in the science of radiology from the time of Roentgen's discovery, to the period of this congress" (First American Congress of Radiology) The various chapters are written by men particularly adapted to the given phase they treat The space is well allocated to the various aspects of radiology, including history, physics and all branches of medicine affected The correlation of x-ray and radium therapy which are inseparable in clinical application, is well brought out,—a valuable feature in a treatise of this character The full bibliography adds value to the book as a work of reference It is so interestingly written that it reads almost like fiction, yet it includes a vast amount of information

G E W

The Doctor and Citizenship By THURMAN D KITCHIN 89 pages, 14 x 20 5 cm Christopher Publishing House, Boston 1934 Price, \$1 50

Dr Kitchin practiced medicine for some years and then was made Dean of the Medical School of Wake Forest College and more recently he was chosen as president of the College His book consists of ten articles, partly addresses and partly essays, mostly about medicine and citizenship and kindred topics He stresses the fact that to be a good doctor the physician must be a good citizen as well It may best be described by quoting one of the running heads of the accompanying advertising leaflet, "An inspiring book of medical culture" That tells the story

J R

The Medical Profession and the Public (A collection of ten papers) 112 pages American Academy of Political and Social Science, Philadelphia 1934 Price, \$1 00

This symposium, presented at a joint meeting of the College of Physicians of Philadelphia and the American Academy of Political and Social Science in Philadelphia, February 7, 1934, discusses the whole subject of the physician's relation to the public The problem from the physician's standpoint is discussed by Drs Nathan B Van Etten, Henry E Sigerist, Grant Fleming, Roger I Lee Morris Fishbein, and Thomas Parran, Jr The sociological side of the question was discussed by the following Messrs James H S Bossard, Edgar Sidenstricker, Michael M Davis and William T Foster

Throughout the symposium the reader will find a good many stimulating comments, many of which he may not agree with The first speaker emphasizes the trend toward socialized medicine While in general this is the stand taken by the lay speakers the physicians on the program took a position against it The last speaker emphasizes What the public does demand is the right to say not how medicine shall be practiced but how it shall be purchased and paid for and who has a better right than those who do the paying? In any event, it is folly to burden physicians any longer with business affairs which they have notoriously mismanaged, and for which they are not trained in which they are not interested and which interfere with that single-hearted devotion to patients which is the glory of their profession"

Fishbein, as the last speaker for the medical profession, states "It is conceivable that out of many of the experiments that have been made and are being made, out of the scientific advancement of medicine itself, there may be a greater and greater tendency toward discounting individuality in medical care. The medical profession feels that the sick man is still an individual, a human being. It has shown repeatedly its willingness to work with economists, sociologists and statesmen toward schemes for making such individual medical care feasible for the vast majority of our people."

J L McC

COLLEGE NEWS NOTES

Acknowledgment of the following gifts to the College Library of publications by members is herewith made

Dr Walter L Bierring (Fellow), Des Moines, Iowa—one reprint,
Dr John M Dyson (Associate), Hazelton, Pa—one reprint,
Dr Dunne W Kirby (Associate), Philadelphia, Pa—6 reprints,
Dr Samuel A Shelburne (Associate), Dallas, Texas—5 reprints

Dr Warfield T Longcope (Fellow), Baltimore, Md, has been elected a member of the board of scientific directors of the Rockefeller Institute for Medical Research, succeeding the late Dr William H Welch

Dr Walter L Bierring (Fellow), Des Moines, Iowa, Dr Benjamin H Orndoff (Fellow), Chicago, Ill, and Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, are among the distinguished guest speakers on the program of the Omaha Mid-West Clinical Society at its annual assembly in Omaha, October 29 to November 2

At the tenth annual meeting of the American Association of the History of Medicine, held some months ago in Cleveland, the following Fellows of the College were elected as indicated

Dr E B Krumbhaar, Philadelphia, Pa, *President*,
Dr W S Middleton, Madison, Wis, *Vice-President*,
Dr E J G Beardsley, Philadelphia, Pa, *Secretary-Treasurer*,
Dr Carl V Weller, Ann Arbor, Mich, *Member of the Council*

Dr J Gurney Taylor (Fellow), Milwaukee, Wis, has been appointed Chairman of the newly organized subsidiary board for Part III of the National Board of Medical Examiners

Dr Virgil H Cornell (Fellow), Curator of the Army Medical Museum, has been reelected Secretary of the National Institute of Health for the coming year

Dr S A Slater (Fellow) Worthington, Minn, has been elected President of the Southern Minnesota Medical Association for the forthcoming year. Dr Charles W Mayo, Rochester Minn was elected First Vice-President, Dr J C Michael, Minneapolis Minn Second Vice-President, and Dr H C Haben (Fellow), Rochester, Minn, Secretary

Dr Burton R Corbns (Fellow), Grand Rapids, Mich became Acting Secretary of the Michigan State Medical Society on September 1, 1934

Dr Virgil P Sydenstricker (Fellow), Augusta, Ga, gave the lecture on the "Treatment of the Anemias" in connection with the series of lectures at Sandersville, Ga, sponsored during the past summer by Emory University and University of Georgia under the supervision of the State Board of Health

Dr Wallace M Yater (Fellow), Washington, D C, has been elected Vice-President of the Washington Heart Association

Drs Arthur C Christie (Fellow), J Russell Verbrycke, Jr (Fellow) Thomas A Groover (Fellow), and Henry C Macatee (Fellow) are among those who will serve upon the District of Columbia Health and Hospital Council composed of representatives of the medical, dental and civic societies as recently organized under the sponsorship of the Council of Social Agencies. Ross Garrett, Health Secretary of the Council of Social Agencies, has announced that this newly organized Health and Hospital Council "will be available to all government authority as a medium of ascertaining opinion and reaction of the majority in professional, administrative and lay organizations representing the citizens in the district"

Dr Joseph A Mendelson (Associate) has been retired from active service as Major, Medical Corps, U S Army, Station Hospital, Fort F E Warren, Cheyenne Wyo, because of physical disability. He has planned to return to Tientsin, China, to engage in the practice of Internal Medicine

Dr Henry I Klopp (Fellow), Superintendent and Physician in Chief of the Allentown (Pa) State Hospital, became a Life Member of the American College of Physicians on August 20, 1934

Dr Edward Schons (Fellow), St Paul Minn, retiring President of the Minnesota Radiological Society, addressed the joint meeting of the Minnesota Radiological Society and the Minnesota State Medical Association at Duluth, July 16, 1934, on 'The Value of Cholecystography by the Oral Route, with an Analysis of 189 Operated Cases'

On September 1, 1934, Dr H Beckett Lang, heretofore Director of Clinical Psychiatry at the Marcy State Hospital, Marcy, N Y, became Director of Clinical Psychiatry at the Pilgrim State Hospital, Brentwood, Long Island

Dr Daniel F Milam (Fellow) has been transferred to Panama by the International Health Board of the Rockefeller Foundation

Dr James L McCartney (Fellow), who for the past three years has been Psychiatrist and Director of Classification under the New York State Department of Correction at the Elmira Reformatory, resigned from that position September 1, to enter the private practice of neuropsychiatry in Portland, Oregon. Under a grant from the New York Academy of Medicine, Dr McCartney has written a book on the classification of prisoners which is now in press.

A PLAN TO EVALUATE INDEPENDENTLY SEROLOGIC PROCEDURE FOR THE DIAGNOSIS OF SYPHILIS IN THE UNITED STATES

Since the serologic conferences at Copenhagen and Montevideo, there has been an increased interest in the relative value of serologic tests for the diagnosis of syphilis. At these conferences the test of only one serologist of the United States was presented for consideration. There are a number of excellent serologists in this country, many of whom have described original modifications of the complement-fixation and precipitation tests for syphilis. It is felt that the tests of these workers merit consideration.

The United States Public Health Service is cooperating with the American Society of Clinical Pathologists in the drafting of a plan to evaluate independently serologic procedure for the diagnosis of syphilis in this country. Briefly, the plan contemplates the collection of specimens of blood from at least 1,000 individuals and the distribution of comparable specimens to the laboratories of serologists who have described an original modification of a complement-fixation or precipitation test for the diagnosis of syphilis. The donors of the specimens will be carefully selected so as to measure both the specificity and sensitivity of the serologic procedure. The sending of specimens to workers at considerable distance from the point of collection will be expedited by the use of the most modern transportation facilities, while the delivery of specimens to nearby serologists will be delayed so as to make the delivery time approximate that for those workers at the more remote points.

A committee of five members consisting of two specialists in the field of clinical syphilology, two members of the American Society of Clinical Pathologists, and one officer of the United States Public Health Service will organize the plan of study and, after all laboratory reports have been submitted by participating serologists, will interpret the results on the basis of clinical findings. The collection of the specimens will begin about December 1, 1934, and a number of serologists will be invited to take part in the evaluation scheme.

It is possible that the name of some serologist who has described an original modification of a test for syphilis may have been inadvertently omitted. Any serologist desiring to participate will be extended an invitation upon presentation of suitable proof as to the originality of his modification of a serologic test. A brief description of the plan will also be sent to those workers who may be interested.

Correspondence should be addressed to the Surgeon General, United States Public Health Service, Washington, D. C.

OBITUARY

DR JAMES LESTER JUNK

Dr James Lester Junk, of Connellsville, Pa, died May 20, 1934, as the result of a ruptured abdominal aneurysm, after an illness of but a few days. He was 54 years of age, having been born October 3, 1879, at the Junk homestead at Laurel Hill, in Fayette County. After attending grade school, he first entered California State Teacher's College, and, later, Pennsylvania State College. It was at State College that his proficiency at football first began to attract the wide attention which, later, at the University of Pennsylvania, where he studied medicine, won him the signal honor of a place on Walter Camps All-American team of 1905.

Dr Junk graduated from the Medical School of the University of Pennsylvania in 1907, with highest honors, and after serving in a Philadelphia hospital and finishing a postgraduate course at Harvard Medical School, began the practice of his profession at Dunbar, Pa, in 1908, removing after four years to Connellsville.

During the war he held a commission as first lieutenant, and was in charge of the base military hospital at Aberdeen, Maryland. Later he joined the National Guard, and was appointed Major in the Medical Corps in 1922, which rank he held until his death.

Always deeply interested in children and their education, he served for years on the Connellsville Board of Education, holding the office of President for five consecutive years. In 1909 Dr Junk married Miss Janet Handlin, of Dunbar, Pa. Mrs Junk died in 1914. Dr Junk is survived by his mother and four brothers.

He was a past president of the Fayette County Medical Society, and was also a member of the Pennsylvania State Society, of the American Medical Association, and had been an Associate of the American College of Physicians since December 30, 1921. He belonged to the Sigma Alpha Epsilon fraternity and was a Mason.

So high a place did Dr Junk occupy in the regard of his community, both as citizen and physician, that all united to show him honor. His body lay in state in the State Armory, and every medical, fraternal, educational and civic group of that section took action to pay their final respects. Many of the stores of the city closed during the services—all attesting to the deep regard and appreciation in which he was held, and to the sorrow felt at the ending of a life so full of usefulness and devotion to others.

E BOSWORTH MCCREADY, M D , F A C P ,

Governor for Western Pennsylvania

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CLINICO-PATHOLOGIC OBSERVATIONS ON INFANTILE PARALYSIS REPORT OF 125 ACUTE CASES WITH SPECIAL REFERENCE TO THE THERAPEUTIC USE OF CONVALESCENT AND ADULT BLOOD TRANSFUSIONS. THE POSSIBLE RELATION OF BLOOD GROUP TO THE SEVERITY OF THE DISEASE*

By D MURRAY COWIE, M D, F A C P, J P PARSONS, M D,
and K LOWENBERG, M D, *Ann Arbor, Michigan*

DURING the Michigan infantile paralysis epidemic of 1931 (figure 1) 125 cases came under our observation. Eighty-one of these were first seen in the so-called systemic or pre-paralytic stage, 44 in the paralytic stage. All of the systemic cases received either convalescent poliomyelitis serum, convalescent whole blood, adult whole blood or a combination of these by the various administration routes. Four of these developed paralysis. One was not under our control and is omitted from the total number, leaving 80 treated cases for analysis. Seventy-seven of these, or 96 per cent, did not develop paralysis. In the three patients developing paralysis the involvement was slight, and recovery was complete at the end of one month of convalescence. No case in this series shows any paralysis today.

Of the paralyzed cases, 27 received immunotherapy as soon as they came under observation. Nine of these (33⅓ per cent) showed definite improvement (three completely recovered), 18 cases (66⅔ per cent) showed no improvement (five died). Seventeen paralyzed cases received no immunotherapy, 12 per cent improved, 89 per cent showed marked residual paralysis.

Criteria upon Which the Diagnosis Was Based Symptoms: Fever, headache, vomiting, diarrhea, constipation, tremor, irritability, drowsiness, sweating, disturbance of breathing and swallowing, dromedary phenomenon. Physical findings: stiff neck, stiff back with or without pain, normal, hyperactive, or lost, tendon cremasteric and abdominal reflexes, spinal fluid

* Presented at the meeting of the American Pediatric Society at Rochester, Minnesota May 1932.

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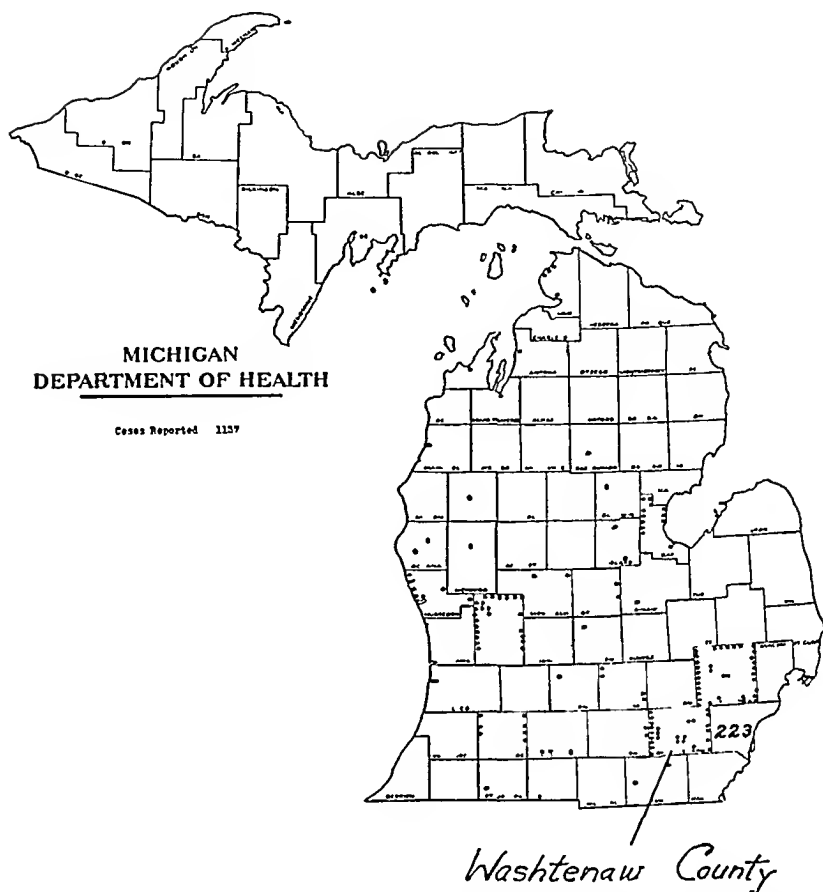


FIG 1 Michigan Poliomyelitis Epidemic 1932 Cases reported 1132 Greatest concentration Washtenaw, Wayne (223 cases), Livingston (N E), Jackson (N W), Ann Arbor center of Washtenaw

changes (pressure, cell count and cell type, globulin mastic and colloidal gold tests), blood count

Personnel All persons connected with this investigation may be considered to have been expert in the work done by them. That is, those examining spinal fluids had had much experience before assisting in the epidemic. The large majority of the counts were made by one man and checked by several others. Those giving intraspinal injections of serum, blood transfusions, and intravenous glucose had also had much experience with this type of work. Blood typing and cross blood typing were done with great care by experienced workers. The physical examinations were carefully conducted and verified. A member of the Department of Anatomy and Orthopedics made complete and almost daily muscle studies on the large majority of the cases, spending practically his entire time at the Contagious Hospital.

Technic in General The very large majority of treatments were

given in well equipped operating rooms. Most of those patients desiring to remain in their homes were taken to the hospital for their treatments. Those who for some reason could not come to the hospital were cared for at home with scrupulous aseptic technic. A microscope and facilities for blood typing and cross typing were taken to the home.

Cooperation Perhaps more complete cooperation of the entire citizenry of a community than that shown in our immediate vicinity has never been seen. Anticipating an epidemic of magnitude, a conference was called August 20, and the organization known as the Michigan Commission on Infantile Paralysis was formed. The Commission was financed by the State Medical Society \$1,000, the W. K. Kellogg Foundation \$4,500, and the Couzens Children's Fund \$4,500, making a total of \$10,000, the amount estimated necessary to carry out the program. The State was divided into districts, each presided over by a physician chosen by the Commission. Serum was pooled at the State Department of Health and sent to the Commissioners who distributed it free of charge to all indigents and to those who for any reason were unable to pay the otherwise nominal charge. From 460 paid donors, 35,195 c c of serum were produced, and 21,530 c c were distributed. We are indebted to Dr. C. C. Slemons, State Commissioner of Health, for these figures. The Commission cooperated in every way possible, assisting physicians and defraying expenses for careful medical services. There was no citizen in the State deprived of the best medical care procurable.

Educational campaign lectures were given in the various towns and districts. The press cooperated splendidly in keeping the people informed on how to recognize the disease and how to secure proper service. In our own vicinity, the schools were not opened until the epidemic was well under control. The theaters, churches and Sunday Schools admitted no children. The book stores developed a method of school book purchase and distribution that excluded children from their stores. The press gave daily information on the epidemic urging parents to have their children carefully observed for any manifestation of ill health. Physicians and all people interested in public health were in every way cooperative.

There were naturally many cases observed that were not suggestive of poliomyelitis. On the other hand, we saw many cases with fever, digestive upsets, headaches, etc., which on careful watching did not develop the neck and spine signs, but which may have been abortive forms of the disease. No serum was given to these and no record of them is included in this report.

All the information possible was given the public concerning the high incidence of protection afforded by the immunological treatment as reported by various observers. It seemed to us that there was no one in our immediate community who did not have an intelligent idea of the epidemic. Any fear acquired by this knowledge was legitimate. There was little or no panic. On the other hand, there was a certain confidence

that if the disease was recognized early it could be checked or modified by the use of serum. The difference of opinion concerning the value of serum was kept alive by those who did not favor its use. This apparently had no effect in the response of the public to the advice of the Commission.

CLINICAL OBSERVATIONS

GROUP A SYSTEMIC CASES

Analysis of 80 cases treated during the pre-paralytic or so-called systemic stage of the disease

Age The ages varied from 1½ to 45 years. 92½ per cent of the cases were between 1½ and 15 years old.

Fever All the cases showed fever. The temperatures varied from 101° to as high as 105° F. In 22 per cent it was high, in 32 per cent moderate, in 46 per cent slight. It was moderate or slight in 46 per cent, in which group the three cases of paralysis occurred. The dromedary phenomenon was present in 21, or 26 per cent.

Headache Headache was complained of in all but four cases. These patients were too young to complain.

Vomiting Vomiting was present in 43 cases (53 per cent), diarrhea in 12, or 14 per cent, constipation in 26, or 32 per cent.

Tremor Tremor was observed in 13, or 16 per cent. *Irritability* was noted in 8, or 10 per cent, *drowsiness* in 29, or 36 per cent, *sweating* in 19, or 23 per cent, *neck sign* in 74, or 91 per cent, *spine sign* in 79, or 99 per cent. The *reflexes* were hyperactive in 37, or 45.5 per cent, diminished in 5, or 6 per cent, absent in 7, or 8.5 per cent. The *bulbar type* of the disease was seen in 3 patients, or 3.6 per cent. The *spinal type* in 78, or 96 per cent.

The *spinal fluid cell count* was increased in 78, or 96 per cent. Of the three in which counts were not made, one had otherwise marked manifestations and her sister similarly affected had a spinal fluid cell count of 60. One case, a girl of five years, who was exceptionally irritable, showed marked neck and spine signs, all reflexes hyperactive, headache, vomiting, diarrhea, and fever of 102° F. It was thought best not to do a spinal tap on this patient. The third case, a girl of eight, who had unquestioned manifestations, had a sister with similar manifestations whose spinal fluid showed a cell count of 105.

In 53 cases the spinal fluid cell count was done once. The counts in these cases varied between eight and 1200, in only eight cases was the count below 20. Counts were done twice in 16 cases, they varied between four and 350. In two cases counts of four and eight cells, respectively, were found, in each of these globulin was positive. Counts were done three times in four cases. They were as high as 1200 declining to 150, 950 declining to 19, 90 declining to 6, and 207 declining to 22, respectively.

The *spinal fluid globulin* test was positive in 46 cases, and negative in

28 of the 74 cases in which it was done. In 11 of the latter a check observation was made at a subsequent time. The result was the same. Only once was globulin negative when the mastic test was positive, only twice when the colloidal gold test was positive.

The *spinal fluid mastic* test was done in 39 cases. It was positive in eight, negative in 31. The reaction varied from 011000 to 344222.

Treatment Twenty-one cases received immunotherapy as early as the second day, 16 the third day, 17 the fourth day, 12 the fifth and sixth days, seven the seventh and eighth days, four the ninth and tenth days, one the thirteenth day and one on the fifteenth day of the disease. Eighty-six and one-half per cent of the cases in this group received treatment between the second and sixth days of the disease. The three cases in which paralysis occurred were treated on the seventh, second and third days of the disease, respectively. One of these received 50 c c of convalescent whole blood intramuscularly, one was given a transfusion of 125 c c of adult blood, 20 c c of convalescent serum in the muscle and 10 c c in the spine, and one received a transfusion of 175 c c of adult blood and 20 c c of convalescent serum in the vein.

In compliance with the request of the Poliomyelitis Commission most of the cases treated outside the hospital received serum intraspinally or intravenously. Only a few of those treated in the hospital were given serum intraspinally. The dose used intraspinally varied between 6 c c and 20 c c, and was given after preliminary removal of a similar amount of spinal fluid. The intravenous dose varied between 10 c c and 60 c c, the intramuscular dose between 20 c c and 50 c c. Convalescent blood transfusions were given to as many patients as possible. The amount of blood varied between 100 c c and 225 c c. Less than 150 c c was given in three cases only, 200 c c and over in 11 cases. Adult blood transfusions were given in the same amounts. One patient with bulbar symptoms, was given 325 c c of adult blood.

The methods of administration of serum and blood are classified in table 1.

Intravenous glucose, in 20 per cent and 50 per cent solutions, was given in nine cases because of special symptoms, referred to later. The amount varied from 100 c c of the 20 per cent solution to as high as 200 c c of the 50 per cent solution.

The report of the Michigan Commission on Infantile Paralysis⁴⁰ (1931) shows that in a selected group of 233 cases in which *convalescent serum* treatment was given during the pre-paralytic stage, 181, or 76.6 per cent, recovered without developing paralysis, and 52, or 22 per cent, developed paralysis. This is in marked contrast with our series in which 96 per cent recovered without paralysis and 100 per cent developed no permanent palsy. Our series differs in that transfusions of convalescent and adult blood were given in addition to convalescent serum in a large percentage of the cases. This may be responsible for the lower paralysis rate in our series.

TABLE I

Method of Administration of Immunotherapy in the 80 Cases under Complete Control *

| | Cases |
|--|----------|
| Convalescent serum alone in the vein | 13 |
| “ “ “ in the muscle | 5 |
| “ “ in the vein and spine | 9 |
| “ “ in the muscle and spine | 1 |
| “ “ in the vein and muscle | 1 |
| “ “ in the vein, spine and muscle | 3 |
| Convalescent blood transfusion alone | 7 |
| “ “ and serum in the vein | 6 |
| “ “ and serum in the muscle | 5 |
| “ “ and serum in the spine and muscle | 1 |
| “ “ and serum in the vein and muscle | 2 |
| “ “ and serum in the spine and vein | 1 |
| Adult blood transfusion alone | 10 |
| “ “ and serum in the vein | 8 |
| “ “ and serum in the muscle | 5 |
| “ “ and serum in the spine and muscle | 1 |
| “ “ and serum in the vein and muscle | 1 |
| Convalescent whole blood in the muscle alone | 1 |
| | <hr/> 80 |

* Transfusions were given in 48 cases, 60 per cent

It is of interest to record the protocols of the paralyzed cases, including the patient who was not under our complete control. They are as follows

CASE REPORTS

Case 78 Anna W, age 2, was taken ill August 15, 1931, with symptoms suggestive of poliomyelitis. This diagnosis was made before entrance and no details are obtainable. On admission August 21, 1931, six days later, the seventh day of the disease, she did not appear acutely ill. There were none of the usual symptoms except those elicited on physical examination. There were pain and stiffness of the neck and back. The left knee jerk was diminished, the right hyperactive. The spinal fluid cell count was 30, mastic and colloidal gold negative, globulin ++++. She was given 50 c c of convalescent serum intramuscularly.

On the tenth day (August 25), the cell count was 20, mastic 111000, colloidal gold 0111110000, globulin ++++. Between this date and the thirteenth day she developed weakness of the abdominal muscles and paralysis of the left gastrocnemius, dorsal flexors, quadriceps and ham string muscles. She was discharged on the thirty-ninth day, September 28, 1931. There was some residual paralysis of the muscle groups described. This, however, completely cleared up in a short time. We should have transfused this patient. Most of the cases coming in as late or later than this one were given more intensive treatment. On the other hand, there were four cases that received about the same treatment and all of them recovered without the development of paralysis, all had marked symptoms.

Case 79 John D, age 6, was taken ill on August 25, 1931, with severe headache, pain in the neck and back and slight fever. Soon after this he became dizzy and vomited when he sat up. He complained of pain in the temporal region if he raised his arms. The bowels were constipated. Examination was negative except for stiffness of the neck and back and pain in the back on bending forward. The reflexes were hyperactive. He was admitted to the hospital at midnight on this date. The spinal fluid cell count was 1200, mastic negative, colloidal gold 0122100000, globulin negative. He was given 20 c c of convalescent serum intramuscularly, and the following morning 10 c c intraspinally. Three minutes after this he developed acute abdominal pain, screamed, and tossed about the bed. The pulse became weak. Gen

eral cyanosis developed and there was a board-like rigidity of the abdomen, spasticity of the lower extremities and marked priapism. Throughout the attack there was excessive thirst. In 45 minutes the attack was over. Soon after this he was given a 125 c c adult blood transfusion.

The course of the illness was otherwise uneventful until the day of discharge, the twenty-third day of the disease. At this time it was observed that the gait of his right foot was not quite normal. This became normal in the course of a few days. We are unable to determine the date of the palsy. His muscles were carefully examined almost daily. The day of discharge his cell count was still high, being 110, the globulin ++++, mastic 111000, colloidal gold 1122210000. This patient has no residual palsy.

Case 80 James T, age 5, was taken ill about 6 00 a m September 2, 1931, with stiffness of the neck and back, vomiting, severe headache, sweating and constipation. A spinal tap was done. The cell count was 700, globulin ++++. He was given 15 c c of convalescent serum in the spine and 45 c c in the vein at 5 00 p m (second day of disease). We advised giving a blood transfusion and an intravenous glucose injection that night. This was not done. He was brought to the hospital the following morning at 10 00 a m (third day). Orders had been left at the ward to give 50 c c of 50 per cent glucose and a blood transfusion on entrance. This was not done. A neurologic consultant felt that poliomyelitis was not present, and active treatment was not carried out. The patient seemed to be fairly well during the day, but toward night difficulty in swallowing developed. The following morning (fourth day) when we first saw him these symptoms were exaggerated and there was general cyanosis from bulbar involvement. Fifty c c of 50 per cent glucose were given intravenously and he was put in the respirator. He died within a few hours. The autopsy record is presented later.

Because stiffness of the neck and back were the earliest signs observed, it is not at all improbable that there had been symptoms previous to this time (dromedary phenomenon) and that the treatment was given later than recorded above. A brother of this child had been ill a week previously with suspicious signs of poliomyelitis, i e, headache, disinclination to play, and some pain in the neck. The symptoms, however, were ephemeral. The father, a physician, had been taking care of poliomyelitis cases. A purely neurological opinion during the early stage of the disease is of little or no value. If reliance is placed on it, it may be definitely harmful.

This case is omitted from the series of 81 because it was not completely under our control. We cannot say that this patient would have lived had the prescribed treatment been carried out. Two other cases showing bulbar symptoms lived. They were more intensely treated. One of these, number 12, is of special interest (page 529), and is recorded later.

Case 81 Grace C, age 7, was taken ill October 4, 1931, with sore throat and fever, which cleared up the following day. Fifteen hours before admission to the hospital on October 7, the third day of the disease, the temperature rose again. The patient became very restless and irritable. Later she became drowsy and complained of headache and pain in the right side of the body, particularly in the right leg. When the leg was extended she would cry out. There was no stiffness of the neck but the spine was stiff. The reflexes were all hyperactive. A spinal tap showed 4 cells, globulin, mastic and colloidal gold tests were negative. She was given 20 c c of convalescent serum in the vein on entrance and six hours later a transfusion of 175 c c of adult blood.

On the fourth day, October 8, careful examination showed extreme muscle tenderness and some weakness of the quadriceps on the right side. On October 13, the ninth day of the disease, reexamination showed no muscle tenderness, palsy or weakness. In this case the serum was given early. The spinal fluid was negative but the symptoms were marked.

GROUP B PARALYZED CASES TREATED AFTER PARALYSIS DEVELOPED

There are 27 paralyzed cases that were given immunotherapy as soon as possible after entrance. These are summarized in table 3. They are grouped together with special reference to the day of the palsy on which they were treated. *Ten were treated on the first day*, of these two completely recovered, two showed definite improvement with only slight residual palsy, four showed no recovery and two, both bulbar cases, died. *Four were treated on the second day*, of these two definitely improved, showing only slight residual palsy, the other two, marked cases, showed no improvement. *Four were treated on the fourth to the fifth day* of the palsy, one of these completely recovered, one, a bulbar case, showed marked improvement with only a slight residual facial palsy, one showed definite improvement and one showed no improvement. *One case treated on the seventh day* was not benefited. Of the remaining eight cases, treated between the thirteenth and the twenty-ninth days of the paralysis, two bulbar cases died, the others showed no improvement.

Of this entire group, three completely recovered. They were treated on the first to the third day of the palsy. Six were definitely improved. This makes a total of nine cases, definitely improved (33½ per cent).

GROUP C PARALYZED CASES NOT TREATED

There were 17 paralyzed cases that did not receive serum. Two improved (12 per cent). Fifteen (88 per cent) showed marked residual paralysis with little or no recovery after entering the hospital. The ages in this group vary from two to 48 years.

If we compare the paralyzed cases that were treated not later than the fifteenth day of the disease with those not treated at all, thus bringing them into line with a similar division treated in the systemic stage of the disease, we have the following results:

TABLE II

| 23 Treated Paralyzed Cases | | 9 Untreated Paralyzed Cases | |
|----------------------------|-------|-----------------------------|-------|
| Improved | 64.3% | Improved | 28.5% |
| Not improved | 33.7% | Not improved | 71.5% |

Intravenous glucose was used in 20 and 50 per cent solutions in 15 cases for relief of headache, pain, muscle tenderness and particularly for bulbar symptoms. The following case we think illustrates benefit from its use.

CASE REPORT

Case 12 Nelson U, age 8, was taken ill on October 2, 1931. He returned home from school in the afternoon with a severe headache. He had complained of being ill during school hours. He then vomited, complained of pain in the back and neck, and of increasing headache. We saw him at 5 00 p m. We regarded the case as an ordinary case of poliomyelitis. There was characteristic stiffness of the back and neck and the reflexes were hyperactive. At 7 00 p m the clinical picture had changed. The temperature had reached 103°. He was stuporous. A spinal tap showed 35 cells, globulin ++++. He was given 6 c c of convalescent serum into the spine and 30 c c in the vein. He continued to grow worse, the stupor increased, and he became wildly delirious. At times he screamed out with pain apparently in his head. At this time, 10 00 p m, we gave 75 c c of 50 per cent glucose in the vein. Soon after this his delirium was less, he stopped screaming and became quiet. He seemed to fall into a natural sleep but the breathing was not normal. It became very rapid, reaching 60. In a few minutes it became slow, irregular and difficult. There was also difficulty in swallowing. Three hours later, 1 00 a m, October 3, we gave him 150 c c of convalescent whole blood in the vein. Within an hour the situation seemed improved but the breathing difficulty still gave us concern. Two hours later generalized convulsions, rigidity and opisthotonos developed. Ten minims of adrenalin were given at this time for fear that allergy might be playing a part in the reaction. This was followed in a few minutes by 50 c c of 50 per cent glucose. The patient relaxed for a while but in a very short time relapsed into convulsions and became cyanotic. We brought him to the Contagious Hospital at this time. His temperature was 104° F, pulse 140, respirations 40. He was given 50 c c of 50 per cent glucose in the vein, 1/8 gr morphine and 1/200 gr atropine sulphate. The convulsions ceased in an hour's time, and at 8 00 a m he was rational. He made an uneventful recovery.

It is our impression that the intravenous glucose (87 grams) was largely responsible for the beneficial results in this case which showed marked manifestations of bulbar involvement. One must also consider the osmotic pull of the blood transfusion as an auxiliary to the glucose. The serum was given early. It did not prevent the occurrence of severe bulbar symptoms. Bulbar manifestations were present at the time the convalescent blood transfusion was given.

We had two quite severe reactions following the use of intraspinal serum. The one just recorded, and case 79. In all, 26 cases received serum by this route. The subject is discussed later.

The Possible Relation of Blood Group to the Severity of the Disease
We have records of the blood type or group in 22 pre-paralytic cases and in 19 paralytic cases. The Moss numerical system of notation is employed in the University Hospital (Groups I, II, III, IV), corresponding to the O, B, A, and AB groups, respectively. Of 130 donors, mostly University students, 27 per cent fell in Group I, 35.8 per cent in Group II, 10.5 per cent in Group III, and 51 per cent in Group IV.

Of the 22 pre-paralytic cases, there were 11, or 50 per cent, in Group IV (AB), six, or 27 per cent, in Group III (A), four, or 18 per cent, in Group II (B), and one, or 4.5 per cent, in Group I (O).

Of the 19 paralytic cases there were five, or 26 per cent, in Group IV (AB), three, or 15.7 per cent, in Group III (A), 10, or 52 per cent, in Group II (B), and one, or 5.26 per cent, in Group I (O).

It is of interest, even though the number of cases is small, to note that of the mild or pre-paralytic cases by far the greatest number fall in Group IV, and 77 per cent of them in the combined Groups IV and III, while of the severe or paralyzed cases by far the greatest number fall in Groups I and II (57 per cent). Setting these figures side by side the comparison is better seen.

Mild poliomyelitis, pre-paralytic—77 per cent, Groups IV and III

Severe poliomyelitis, paralytic—57 per cent, Groups II and I

While we have no right to come to a definite conclusion, it is suggestive from these observations that blood Groups IV and III are the most favorable groups and that blood Groups II and I are the most unfavorable, that is, an individual having a Group II or Group I blood may be more likely to have a severe poliomyelitis than an individual with a Group IV or Group III blood.

Our attention is called to the interesting observations of Jungeblut³⁰ on blood group neutralizing power in poliomyelitis cases. Our results seem at variance with his. Further observations in progress may throw more light on this subject.

PATHOLOGICAL OBSERVATIONS

Acute Cases

Case 80 (James T.) We were able to secure only a small section of tissue from the thoracic cord in this case of marked bulbar poliomyelitis, the clinical history of which has been given earlier.

The gray substance was completely destroyed, containing but a few scattered ganglion cell remains. The nervous tissue was flooded by Hortega elements, astrocytes, lymphocytes and occasional plasma cells, but no leukocytes were present (Figure 1). Countless neuronophagias indicated graves of parenchyma elements. Small foci of necrosis were frequent. The blood vessel system was greatly involved and there were numerous small inflammatory foci in the white matter. There was a pronounced acute meningitis.

Case 86 Virgil P., a seven year old boy, came to the Hospital on what was considered to be the third day of the disease. Inquiry leads us to believe that the prodromal phenomenon was present in this case as there was evidence of indefinite symptoms several days previously. On admittance there was moderate fever, drowsiness, breathing and swallowing difficulty, absence of right biceps reflex and a spinal fluid cell count of 2,300. The diagnosis of bulbar poliomyelitis was made. The patient received 150 c.c. adult blood and 300 c.c. 50 per cent glucose intravenously. He died on the first day in the Hospital.

Brain The leptomeninges are thin and smooth but their blood vessels are enormously dilated and injected. The leptomeninges are bright red in color. Basal vessels are delicate. On frontal sections gray matter is of normal width, of a bluish pink color and the vessels are injected. White matter contains numerous blood points (hyperemia). It is slightly pinkish. The basal ganglia are distinctly outlined and of the same color and appearance as the gray matter. There is a particularly distinct injection of the blood vessels in the medial nuclei of both thalami. A similar condition can be seen in the substantia nigra. All gray nuclei of the subthalamic region, pons and medulla are of a pinkish color, their vessels being dilated and injected. The ventricles are narrow and the ependyma is smooth. There is a small hemorrhage in the pons near the floor of the fourth ventricle.

The leptomeninges of the spinal cord are of the same appearance as those of the cerebrum. The gray matter of the entire cord is very well outlined and distinctly red in color. The white matter is hyperemic.

Spinal Cord The leptomeninges contain numerous lymphocytes and occasional leukocytes and are somewhat edematous. The inflammation affects the perivascular spaces of the blood vessels of the white matter. The infiltration can be followed up to the gray matter. The white matter itself is edematous and contains fairly numerous foci of proliferated astrocytes and occasional lymphocytes. (Figure 2)

In the gray matter the anterior horns are severely affected, numerous ganglion elements are destroyed by neuronophagia and the remaining ones show different acute toxic changes. The gray matter is flooded with countless Hortega elements and



FIG 2 Multiple neuronophagia in both anterior and lateral horns. Parenchyma entirely destroyed. Blood vessels surrounded by dense infiltrates. Marked infiltration of the meninges in the fissura mediana. Microphotograph / 10. Nissl stain.

astrocytes and the blood vessels are surrounded by dense infiltrates. (Figures 2 and 3)

The inflammation extends also over the posterior and lateral horns in many areas so that the entire gray matter appears to be transformed into a single inflammatory focus.

The affection is not always symmetrical, the one side being frequently less affected than the other.

The distribution of the disease process in the different segments of the spinal cord varies considerably, the thoracic and cervical regions being more severely affected



FIG 3 Multiple neuronophagia in the left anterior horn. Right anterior horn better preserved. Pronounced meningitis and perivascular infiltration in the white matter. Microphotograph $\times 10$. Nissl stain.

than the lumbar. In no segment was the gray matter affected in its continuity and the character of the inflammation was a spotty one.

Medulla and Brain Stem. The affection of the medulla and of the brain stem was studied in sections cut through certain gray nuclei.

At the level of the pyramidal decussation, the histological picture was the same as that observed in different segments of the spinal cord.

On section through the midpart of the olives numerous gray nuclei were found to be affected. Particularly severe was the inflammation in the respiratory area (substantia reticularis), but various other nuclei especially those of the cranial nerves (at this level, nucleus nervi hypoglossi and nucleus ambiguus vagi) were also affected.

The nucleus olivaris inferior remained free; its parenchyma was well preserved. There was no glia activity but a few blood vessels of this nucleus were surrounded by lymphocytic infiltrations. The same condition prevailed in the nucleus olivaris accessorius medialis and dorsalis.

On the level of the entry of the acoustic nerve a similar picture prevailed. There were numerous inflammatory foci in the corpus restiformis, the substantia reticularis and nucleus nervi vestibularis were uniformly involved, the olives again remained free.

Higher up the nuclei nervi facialis and nervi abducens were both affected. The substantia reticularis represented a very active area of inflammation, but the nuclei pontis were altogether spared.

On section through the nucleus nervi trigemini the floor of the fourth ventricle contained countless inflammatory foci, the peak of the inflammation being in the nucleus of this nerve and in the substantia reticularis.

The inflammation could be traced through the entire central gray substance surrounding the aqueduct and in the lateral fields of the substantia reticularis

The intensity of the inflammation subsided somewhat in the lower parts of the corpora quadrigemina, the nucleus nervi trochlearis and the stratum griseum centrale being moderately affected

In the region of the roots of the nervi oculomotorii inflammatory phenomena were seen in a number of formations in the nucleus of this nerve, in the substantia nigra, in the red nuclei, and in the central gray substance. The intensity of the inflammation was moderate

The corpora geniculata lateralia were entirely free at this level but the pedunculi cerebri contained numerous infiltrates, a few thrombosed vessels were surrounded by small hemorrhages

In the hypothalamic region occasional scattered inflammatory foci were present, but the disease flared up again in the thalamus where there were numerous areas of intense inflammation

The pallidum, putamen and caudate nuclei, the cortex and the entire white substance of both hemispheres were free of pathological changes, but the meninges showed pronounced inflammatory phenomena at the base of the brain as well as over both convexities

In all regions examined not all gray areas were affected and in those involved the degree of the inflammation varied greatly at different levels. The distribution of the inflammation in the spinal cord and brain stem was not continuous. It was spotty in character, but the histological character was the same throughout

CASE AUTOPSY SUMMARY

Central Nervous System The inflammation involves the meninges, the gray matter of the spinal cord and brain hemispheres but spares the white and gray substances of the brain

The gray substance of the spinal cord, the brain stem, the walls and the floor of the third ventricle and the thalamus are involved in the disease. It cannot be said that the intensity of the inflammation is subsiding in the brain stem, in spite of the fact that certain nuclei of this region were only moderately involved, since it flares up again in the thalamus

Histologically the disease is characterized by the digestion of parenchyma elements by neuronophagia, intense glia response with formation of astrocytes and Hortega elements and severe generalized involvement of the blood vessel system which is surrounded by dense masses of lymphocytes

Thymus Large, measures 11 by 6 by 2 cm. It consists wholly of lymphoid tissue with the thoracic and cervical lobes well represented. Marked hyperplasia of cortex and medulla. Congestion. Extensive hemorrhage into capsule. *Bronchial Glands* Moderately hyperplastic and show moderate anthracosis. *Cervical Lymph Nodes* Not examined. *Spleen* Measures 10 by 5½ by 2½ cm. Weighs 250 grams. Capsule is rather lax and slightly wrinkled. Section shows abundant lymphoid tissue. Cut surface is red in color. The follicles can be seen with the naked eye. No tubercles. Acute passive congestion. Moderate lymphoid hyperplasia. Lymphoid exhaustion. *Large Intestine* Lymphoid follicles rather prominent. No ulceration. *Small Intestine* Very large and prominent Peyer's patches. No ulceration. No tubercles found in the mucosa. Lymphoid tissue hyperplastic. Congestion. In the lower ileum there is marked catarrh of the mucosa. *Appendix* Lymphoid hyperplasia. *Mesenteric Lymph Nodes* Marked hyperplasia. Three mesenteric lymph nodes near the attachment of the mesentery are almost completely replaced by calcified necrotic material. Congestion. Lymphoid hyperplasia. *Left Adrenal* Marked hypoplasia of cortex and medulla. Right same. (C. V. Weller)

Pathological Diagnosis Acute polioencephalitis Asphyxiative death Petechial hemorrhages beneath epicardium, in the thymic capsule and in the gastric mucosa Pulmonary atelectasis and emphysema Acute purulent bronchitis and early bronchopneumonia Acute passive congestion of all organs Subendocardial fatty degenerative infiltration Thymico-lymphatic constitution (hyperplastic thymus, generalized lymphoid hyperplasia with lymphoid exhaustion, hypoplasia of adrenals and aorta)

In the summary of the general pathology in this and succeeding autopsy records, detailed data of the lymphatic and lymphoid structures only are given Somewhat recently attention has been focused on these structures It should be noted here and will be discussed later that these findings form a familiar picture of the status thymico-lymphaticus

Case 90 Thomas M, 14 year old boy, entered the hospital on the fourth day of the disease and the first day of the palsy His symptoms were moderate fever, headache, vomiting, drowsiness, marked neck signs, positive spine sign, normal knee jerks, hyperactive right biceps reflex The spinal fluid showed 99 cells, globulin three plus, mastic 211000, gold 0122100000 There was marked breathing and swallowing difficulty Diagnosis, bulbar type of poliomyelitis Blood Group IV Thirty cc of convalescent serum were given intramuscularly and a transfusion of 250 cc of convalescent blood, and 200 cc of 50 per cent glucose at a subsequent time There was no abatement of the symptoms

AUTOPSY

Brain The leptomeninges are thin, bright red in color, with strongly injected vessels The convolutions are somewhat flattened out and the consistency of the brain is firm The basal vessels are delicate At the base of both temporal lobes, but especially pronounced on the left side, there is an accumulation of opaque patches resembling somewhat tuberculous lesions The infundibular region and the pons are free from these changes

On frontal sections the gray matter is of normal width, pinkish bluish gray in color, with injected blood vessels It is very distinctly outlined The white matter is hyperemic but otherwise without gross changes The basal ganglia are well outlined and of the same appearance as the gray matter The ventricles are narrow The thalamus, subthalamus, floor of the fourth ventricle and gray nuclei of pons are highly hyperemic The gray matter of all these regions is distinctly pinkish in color

Spinal Cord The gray matter of the spinal cord is distinctly pinkish and because of this it is very well outlined There is considerable edema of the white matter of the spinal cord Its meninges are bright red and their vessels are injected

The histological findings in the meninges and the spinal cord were essentially the same as those of case 86 (Potter)

Medulla and Brain Stem The inflammation involved the medulla with unusual intensity The entire floor of the fourth ventricle was transformed into a large and continuous area of inflammation which rendered the differentiation of the single nuclei impossible The parenchyma was gravely affected and the tissue was flooded by countless neuronophagias, Hortega elements and astrocytes mingled with lymphocytes and leukocytes which migrated into the nervous tissue from the greatly irritated blood vessels (Figure 4)

The inferior olives remained essentially free, their parenchyma being well preserved The intensity of the disease subsided somewhat in the region of the lower corpora quadrigemina but the central gray substance contained numerous inflammatory foci

At the level of the nucleus of the nervus oculomotorius the inflammation was still very distinct in the nucleus of this nerve, but the substantia nigra and the red nuclei were but moderately involved



FIG 4 Anterior horn with scars Destruction of the parenchyma Multiple neuronophagia, pronounced glia response Lateral and posterior horns severely involved Microphotograph $\times 40$ Nissl stain

The inflammation could be continuously traced along the aqueduct and numerous foci were seen in the entire hypothalamic region and the thalamus. The pallidum, putamen, caudate nuclei, the white substance of the hemispheres and the cortex were free from pathological changes, but there was an outspoken acute meningitis at the base of the brain.

CASE AUTOPSY SUMMARY

Central Nervous System The histological picture in this case is characterized by a particularly severe affection of the medulla and brain stem including the hypothalamic region. The sympathetic nervous system is here involved practically throughout.

Thymus Persistent and hyperplastic, about one-third larger than normal for age and size. *Bronchial Glands* Small and black on sectioning. *Cervical Lymph Nodes* Not palpable. *Spleen* Measures 10 by $6\frac{1}{2}$ by $2\frac{1}{2}$ cm and weighs 100 grams. It is purplish red in color. The cut section shows marked congestion and hyperplasia of the lymphoid follicles. Marked passive congestion. Moderate lymphoid hyperplasia. *Large Intestine* Shows moderate congestion, few petechial hemorrhages and hyper-

plasia of the solitary lymph follicles *Small Intestine* Shows slight congestion and marked hyperplasia of Peyer's patches and solitary lymph follicles *Mesenteric Lymph Nodes* Hyperplastic Chronic hyperplastic lymphadenitis with stasis catarrh *Peribronchial Lymph Nodes* Hyperplastic, congested, with slight anthracosis *Adrenals* Hyperplasia of both cortex and medulla *Retroperitoneal Lymph Nodes* Hyperplastic lymphadenitis (C V Weller)

Pathological Diagnosis Acute meningo-encephalo-poliomyelitis of bulbar type Marked congestion, edema and small hemorrhages in brain substance Terminal hemorrhagic purulent lobular pneumonia Pulmonary congestion, edema and emphysema Subepicardial fatty infiltration Right-sided cardiac dilatation with relative tricuspid and pulmonary insufficiency Thymico-lymphatic constitution (hyperplastic thymus, generalized lymphoid hyperplasia, hypoplasia of aorta and adrenals) Passive congestion and parenchymatous degeneration of all organs

Case 100 Letha S, poliomyelitis, acute Entered the Hospital on the nineteenth day of the disease The history reveals the presence of the dromedary phenomenon The clinical record shows as leading manifestations, slight fever, marked headaches, constipation, marked irritability, psychoneurotic reactions, marked retention of urine, neck and spine signs, loss of knee reflexes Spinal fluid showed 160 cells, globulin four plus, mastic 223311, gold 0012222100 Paralysis of both lower extremities, and bladder Died 44 days after the onset of the disease

AUTOPSY

Central Nervous System The leptomeninges are thin and smooth, their blood vessels somewhat injected

On frontal sections, the gray matter is of normal width and appearance, the white



FIG 5 Multiple foci of inflammation in the floor of the fourth ventricle Parenchyma of most of the nuclei almost completely destroyed Olives not affected Microphoto graph $\times 10$ Nissl stain

matter contains countless blood points The basal ganglia are well outlined and without gross changes

The pons is of normal appearance but the medulla shows a pronounced injection of its blood vessels There is a definite hemorrhagic tinge to the gray matter of the spinal cord and there are small hemorrhages especially pronounced in the thoracic region The injection of the anterior horns can be followed throughout the spinal cord and increases again in the lumbar region where there are distinct red foci in the anterior horns

The histological picture of this case differs in many respects from the findings in the two foregoing cases

In the spinal cord there were countless neuronophagias and severe destruction of



FIG 6 Massive inflammation of both anterior horns in the lumbar region Parenchyma completely destroyed Gray matter flooded with countless glia elements and lymphocytes Blood vessels surrounded by massive infiltrations Microphotograph $\times 10$ Nissl stain

the parenchyma The infiltrations of the blood vessel system were unusually massive and consisted mainly of lymphocytes mingled with countless plasma elements and polyblasts Even the finest capillaries were surrounded by these cells which produced histological pictures of unusual intensity The glia response was in keeping with this The inflammation was particularly severe in the lumbar portion of the cord and somewhat less pronounced in the thoracic and cervical regions (Figure 5)

The meninges were thickly infiltrated by lymphocytes

In the medulla and brain stem only certain regions were affected The respiratory area was damaged throughout but the affection was not symmetrical at all levels There were pronounced inflammatory changes in the nucleus nervi vagi and trigemini

The substantia nigra presented quite an unusual degree of change It was affected in the same way and with the same intensity as were the lumbar segments of the spinal cord, and was completely destroyed (Figure 6)

The other nuclei of this region, including the substantia grisea centralis, and the hypothalamic region were practically free of changes but there were numerous foci in the thalamus

In the cortex of both hemispheres, especially in the parietal and temporal lobes, numerous small areas of inflammation were encountered. Their histologic structure was identical with that of the spinal cord lesions

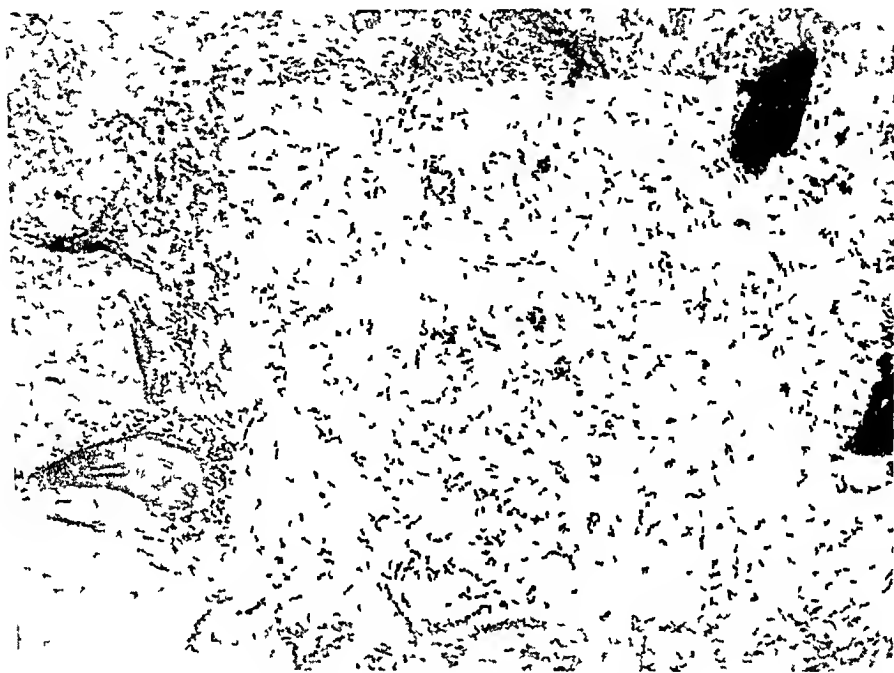


FIG 7 Massive inflammation of the substantia nigra. Tissue flooded with countless glia elements and lymphocytes. Perivascular spaces contain dense infiltrates (lymphocytes and plasma cells)

CASE AUTOPSY SUMMARY

Central Nervous System The distribution of the inflammatory lesions is somewhat atypical in this case. The peak of the inflammation is reached in the lumbar cord, again in the substantia nigra and again in the respiratory area. The hypothalamic region is essentially free as are many areas of the sympathetic system, but large areas of the cortex in both hemispheres are affected. The histologic deviation lies in the character of the infiltrating elements which consist largely of plasma elements indicating an intense inflammatory lesion of some duration.

Lymph Glands Cervicals—no increase in size. *Mesenteric Lymph Nodes* Not found. *Retroperitoneal Lymph Nodes* Not made out because of large amount of adipose tissue present. *Hemo-Lymph Nodes* Not found. *Spleen* Cut section reveals moderate congestion, and slight increase in the amount of lymphoid tissue. The stroma appears to be somewhat decreased in amount. Atrophy, slight lymphoid exhaustion. *Encapsulated tubercles* *Thymus* Fatty atrophy of a persistent hyperplastic thymus. Small petechial hemorrhages in thymic fat. *Appendix* Lymphoid hyperplasia of slight degree. Lumen dilated. *Mesenteric Retroperitoneal Lymph Nodes* Slight lymphoid hyperplasia with sinus catarrh.

Rectum Contains a small amount of fecal matter. The mucosa near the anal orifice shows three or four shallow ulcers. These are irregular in outline. The

borders are slightly thickened. The floor of these ulcers is smooth and red in color. They are all located within 6 or 8 cm. of the anal orifice. The rectal mucosa higher up is negative except for rather marked congestion. (C. V. Weller.)

Lungs. Pulmonary arteries show recent embolism with induced thrombosis. Emphysema and atelectasis are present. Small atheromatous areas exist in pulmonary artery. Old caseating encapsulated tubercles in the bronchial nodes. Fat stain shows no fat emboli.

Pathological Diagnosis. Acute polio-encephalo-myelitis. Subendocardial fatty degenerative infiltration. Circulatory failure. Parietal thrombosis of right auricular appendage with localized interstitial myocarditis. Pulmonary embolism and induced thrombosis. Subepicardial fatty infiltration. Ulcerative proctitis. Aortic atherosclerosis. Colloid goiter. Lipoidosis of adrenals. Thymico-lymphatic constitution (fatty atrophy of persistent hyperplastic thymus, hypoplasia of aorta and adrenals, slight generalized lymphoid hyperplasia). Old tubercles in bronchial nodes and spleen. Passive congestion, moderate atrophy and parenchymatous degeneration of all organs.

It will be of interest to include the findings of two chronic cases, thus showing the characteristics of permanent changes after the lapse of nine and 30 years, respectively, for the purpose of illustrating our discussion on therapy.

Case 1. A boy of nine years and nine months had contracted poliomyelitis at the age of 13 months.

At autopsy the left hemisphere was found to be smaller than the right. The left side of the medulla was atrophic and the cortex of the left hemisphere appeared to be very narrow. Histologic examination showed in the left hemisphere pronounced and widespread degeneration of the parenchyma, numerous areas being almost wiped out. There were no inflammatory changes or tissue response and the blood vessel system was normal. In the atrophic side of the medulla many gray nuclei were destroyed. There were no changes in the cervical part of the spinal cord, the only part of the cord available for study.

Case 2. An entirely different picture was seen in the brain of this case coming to necropsy 30 years after an acute attack of poliomyelitis of the spinal cord. There was a diffuse degeneration and reduction in number of the ganglia cells in the anterior horns where most of the elements were greatly reduced in size and number and deeply stained. The tigroid was still partially visible. Some of these elements were round in shape, others retained the pyramidal form. There were also numerous yellowish weakly stained cells hardly recognizable as parenchymatous elements. Holzer sections revealed considerable glia production in the gray matter. There were no inflammatory phenomena of any kind nor was there any glia response. Weigert preparations failed to show a definite tract degeneration. The medulla and pons were free of changes.

In the substantia nigra a peculiar focal change was seen. The pigmented parenchyma elements were partly destroyed and others were reduced to cell shadows laden with greenish pigment. There were numerous weakly stained greenish nuclear elements, probably also remains of parenchyma. Large astrocytes and proliferating glial nuclei were scattered everywhere. Accumulations of gitter cells were usually present in the perivascular spaces. Finally, there were scattered fragments of black or green pigment. Only a small part of the formation was affected.

Examination of the basal ganglia showed that numerous focal lesions the size of a pinhead and somewhat larger, in which the parenchyma was destroyed, were present in the thalamus. The gray matter of both parietal lobes also contained small foci. They were organized by glia fibers but otherwise there was

CLINICAL COMMENT

It would seem from a study of these carefully observed cases that immunotherapy given in the pre-paralytic stage of acute poliomyelitis must have played a considerable part in bringing about the results obtained. Reference to the spot map of the Michigan epidemic, kindly furnished us by Dr Slemmons, will give the reader an idea of its extent in our immediate neighborhood. Forty-six and one-half per cent of the entire epidemic was concentrated in this vicinity and was contiguous to Washtenaw County, of which Ann Arbor is the county seat. These counties are Wayne (Detroit, the principal city), Oakland, Livingston, Ingham, Jackson, Lenawee, and Monroe. In other words, this was the center of the epidemic.* It is significant that of a group of 80 systemic cases in this area, most of which were intensively treated with convalescent serum and blood transfusions, none is paralyzed today.

There is also some evidence favoring the use of immunotherapy in the early stages of paralysis. It would seem from the progressive nature of the disease that this practice should be encouraged. It was a common observation to see the paralysis extending over a period of days and there are many reports in the literature in confirmation of this characteristic of the disease. Relapses of the disease are well known. One of our autopsied cases demonstrates this unusually well (case 100, page 536). We had regarded this patient as having fully recovered from the acute stage of the disease. It will be recalled that she did not enter our service until the nineteenth day of the illness. She died on the convalescent orthopedic service on the forty-fourth day of the disease. Autopsy disclosed a pulmonary embolus and induced thrombosis, which was thought to be the cause of death. Microscopic examination of the brain showed extensive acute inflammation in the respiratory center, sufficient to cause death.

Because of the widely disseminated vascular involvement which is invariably present, it would seem that this disease peculiarly lends itself to treatment directed at the vascular system either by direct intravenous and arterial measures or indirect intramuscular measures. Everywhere in the meningeal involvement the primary change and almost the entire change is vascular, indicating a breakdown of the meningo-vascular barrier. It would seem that intraspinal treatment might easily produce severe damage to the already widely affected parenchyma. The situation is entirely different from that found in a pure meningitis. The purpose of the therapy should be twofold. First, to neutralize the "toxins" by convalescent serum and blood transfusions, thus protecting the parenchyma from further damage. Second, to relieve edema, thus freeing the nervous tissue from excessive inflammatory response.

We are familiar with the fact that these same pathologic changes may result from infection that does not spread via the vascular system. That

* Number of cases per square mile greater

is, infection or exciting cause may travel along a nerve trunk, and there is still other evidence which we will present in a subsequent paper, that infection does not necessarily travel via the blood vessels. However, no matter how the infection travels its result is always perivascular infiltration and glia hyperplasia. With this fact in mind it still seems logical to expect that anti-infectious agents must reach these diseased areas via the blood stream.

Physiologists agree that the cerebrospinal fluid is manufactured by the choroid plexuses and passes into the subarachnoid space from the ventricular system. A small amount of the cerebrospinal fluid is delivered to the subarachnoid space via the perivascular spaces that empty into it. In other words, the flow in the perivascular spaces is toward the subarachnoid space. The pressure in the subarachnoid space is greater than the venous pressure. The fluid is absorbed by the subarachnoid villi into the venous sinuses³⁸. Substances injected into the spinal canal may be recovered from the veins of the neck in from 30 to 40 seconds, from the stomach and bladder in from 10 to 20 minutes.

Our experience leads us to recommend that 20 to 30 c c of convalescent serum in the vein, 20 to 50 c c in the muscle, and a transfusion of 100 to 200 c c of convalescent or adult whole blood be given, if possible, to all definitely diagnosed systemic cases and to those in the early days of the paralysis. As large doses as possible should be given. From information gleaned from the use of serum in the prevention of experimental poliomyelitis in monkeys a concentrated serum is indicated.

We are impressed with the great benefit that may accrue from the use of intravenous glucose, particularly in the bulbar cases, and also at times in the systemic and spinal paralytic stages. Theoretically, it should be beneficial in the pre-paralytic stage because much damage comes from edema, and because of its effect in improving volume blood flow. We have seen headache, pain, muscle tenderness and circulatory collapse relieved or caused to disappear by its use. Increasing the osmotic pressure of the blood by means of intravenous hypertonic solutions aspirates the cerebrospinal fluid from the shrinking brain tissue causing a reverse flow in the perivascular and ventricular systems³⁷.

We are confronted with the request for a satisfactory control for the results we have recorded—for a similarly diagnosed group not treated by immunotherapy. Under the existing circumstances as previously set forth this was impossible.

Perhaps the majority of those who have had much experience with the use of convalescent serum in the treatment of acute poliomyelitis in the pre-paralytic stage are favorably impressed with its action. The favorable literature is quite well known. A few references to it will suffice. Aycock²⁹ (1927), McEachern and Bell³⁰ (the Manitoba epidemic, 1928), Shaw, Thelander and Limper³¹ (the California epidemic, 1928), Aycock and Luther³² (a New England epidemic, 1929), Lomer and Shirreff³³ (the

Ottawa epidemic, 1929), a particularly convincing report, and the general review by Amos³⁴ in 1930

It would, however, seem particularly important to give heed to all constructively critical reports. We must give particular thought to the mature and exacting judgment of Dr Park and his associates. Dr Park³⁵ remarks, after a careful analysis of a large series of cases: "The results of observations on treated and untreated patients in the pre-paralytic stage of poliomyelitis during the 1931 outbreak (New York) do not give any statistical proof that the serum has any value when given in cases after the cells of the central nervous system are involved. By this involvement we mean the exhibition of the various manifestations of the sympathetic nervous system and the changes in the spinal fluid." Dr E L Godfrey³⁶ of the New York State Department of Health, discussing Dr Aycock's paper, questioned the validity of his findings because of the lack of a satisfactory control. We wish to point out the difference in the methods we used in the treatment of our cases, i e, the addition of blood transfusions.

It may be that the question turns on the pivots of earliness of diagnosis, thoroughness of the education of physicians and public, and the strenuousness of propaganda. The management of the Ottawa epidemic offers one of the best examples of this practice. Without a parallel control and even without a large preeducation campaign series of cases for comparison, one is quite easily convinced of the favorable influence of convalescent serum in that epidemic. The same is true of the Manitoba epidemic. Here a parallel control is recorded. Blood transfusions were not given in these series.

It may be that in a community like Ottawa, information of this nature would be more likely to become the possession of the entire public, to be more widely disseminated and better understood than it would be in a very much larger community made up of a greater number of types and nationalities. If we compare the cases in our small community with those of the much larger community represented by 860 cases selected from the State at large by the Michigan Commission, suggestive figures are obtained. Of the latter, 45.1 per cent became paralyzed, 47.7 per cent were not paralyzed. In our series only 3 per cent were paralyzed and all completely recovered. In his final paragraph, Dr Park remarks, "Nevertheless, the uniformly optimistic opinions of those who have not observed untreated patients for a comparison cannot be entirely disregarded." We have recorded these cases with the hope that similarly treated series of cases will be reported, particularly with adequate controls, and that our results may be helpful in the final solution of the question as to whether immunotherapy is of value in the treatment of acute epidemic poliomyelitis. We have called attention to the possible relation of blood group to the severity of the disease. Our cases are too few in number to be more than suggestive.

PATHOLOGICAL COMMENT

We designate the disease process which is characterized by a mesodermal response in conjunction with certain transformations of the neuroglia as encephalitis. This histological symptom complex in encephalitis is a defense reaction in the sense of Aschoff. The histologic criteria in acute poliomyelitis correspond to the following formulations. The mesoderm, that is, the blood vessels of the central nervous system, responds by a production of lymphocytes, polyblasts and plasma cells, and leukocytes are attracted from the blood stream. The glia produces Hortega elements and astrocytes as well as glial nodes. All this is directed against a living virus. *We are therefore dealing with an acute encephalitis.*

The histological picture varies considerably according to the duration of the disease and its acuteness. In stormy cases of short duration considerable numbers of leukocytes may be present. This was noted in case 86. In the majority of the cases however, it is known that the leukocytes disappear within a few days but that occasionally they may dominate the histologic picture. Luksche¹ described a case of acute poliomyelitis with typical distribution of the disease, in which the infiltrating elements were predominantly leukocytes. In the anterior horn the leukocytes formed themselves in dense masses in the gray matter and occupied the perivascular spaces. Hauptli² confirmed the presence of leukocytes in the perivascular spaces as well as in the gray tissue by the oxidase reaction. The same results have been obtained by Wohrmann³. According to Hauptli, the leukocytes are present during the first six days of the disease. This is also in accord with our findings.

The lymphocytes appear at the same time as the leukocytes. They are present during the entire period of acute inflammation. The perivascular infiltrations consist mostly of these cells and they frequently migrate into the gray substance.

The plasma elements for the greater part do not appear in the acute stages. They are more characteristically found in later stages of the disease. They were present in case 100, which terminated fatally 44 days after the onset. They are confined to the perivascular spaces and do not enter the nervous tissue.

The response of the glia and the destruction of the parenchyma is a very impressive finding. A very common type of glia reaction is represented by neuronophagia which is a *phagocytosis* of the *dying ganglia cells* by the proliferating microglia. According to Creutzfeld⁴ and others, this neuronophagia is purely a glial response. That is, leukocytes or polyblasts never appear in these foci, never engage in the process of neuronophagia, and the oxidase reaction is therefore always negative.

The neuronophagia, which is almost always present, indicates heavy destruction of the parenchyma. The parenchyma in poliomyelitis is destroyed within a few days. This is an important fact from the standpoint of therapeutic consideration.

Frequent as the neuronophagia may be, it is not uniformly present. It may be missing even in the most acute stages of the disease. In the observation of Wohrmann³ neuronophagia was absent in spite of marked parenchyma destruction and acute glia response. Sharp and Nelson⁵ had a similar experience.

In very rare instances the glial reaction may be entirely absent, as has been reported by Thomas and Lhermitte⁶. In this case, not even Hortega elements were formed although the ganglia cells were destroyed and the connective tissue response was typical.

The destruction of the parenchyma has naturally attracted great attention and some authors have gone so far as to regard the parenchyma degeneration as independent and preceding the inflammatory phenomena. Recently Hurst⁷ again advanced this view, but it cannot be accepted. As mentioned above, poliomyelitis is an acute inflammation of the nervous system and such a condition is never brought about by ganglia cell destruction. Ganglia cell destruction is the result of an inflammation but not its cause. The alteration of the parenchyma constitutes only a part of the inflammation, the ganglia cells suffer in the same way as do the parenchyma elements of other organs under similar conditions.

In certain cases repeated attacks of acute poliomyelitis have been seen, thus we observed in case 100, in which there was a relapse before the end of the first attack. Still⁸ has reported relapses at intervals of from eight days to 12 weeks. Obviously there occurs in such cases a breakdown of immunity which in poliomyelitis is not always acquired and which is not always a permanent factor. Still describes the case of a child who contracted poliomyelitis at the age of 21 months and suffered a permanent paralysis of the left leg. The second attack at the age of 7½ years left no damage.

Peremans⁹ reports the case of a child of four years and nine months, with a second attack three months and a third attack two years after the first one. The child survived. The second attack may be fatal no matter when it occurs, whether a few weeks after the first onset as in our observation (100) or several years later, as in the case of Marinesco and Draganesco¹⁰. In the latter instance, acute changes of the second attack as well as old scars and parenchyma degeneration of the first were present.

As has been pointed out, the virus of this disease affects the anterior and posterior as well as the lateral columns of the spinal cord, the gray masses of the medulla and pons, of the subthalamie region, and of the wall of the third ventricle. All of these regions contain numerous centers which are a part of the sympathetic nervous system. *Acute poliomyelitis is to a great extent a disease of the sympathetic system.* In the clinical picture even in the acute stages, it will be noted that there are many symptoms which confirm this view, one of the most important features being the disturbance of the respiratory area. The frequency of this type of disturbance is in accord with the frequency of anatomical lesions in this region which was affected in all of our autopsied cases.

According to L  chelle, Baruk and Douady¹¹ vasomotor and sympathetic disturbances may result from the involvement of the lateral horns characterized by pains of radicular type and vasomotor and sympathetic disturbances in the extremities

The frequency of the affection of the sympathetic system has been shown by Wernstedt¹² who examined 6775 cases of the great Swedish epidemic of 1911-1913. He reported numerous instances of accommodation, bladder and anal sphincter palsies, as well as those of the lips, tongue and vocal cords

In other instances the involvement of the sympathetic nervous system is restricted to certain brain stem nuclei. A great deal of attention has been paid to isolated facial palsies frequently occurring in epidemics of poliomyelitis, a number of which were observed in this series. Radovici¹³ saw 15 cases and Stern¹⁴ had a similar experience. The isolated affections of the abducens (sixth) and motor oculi (third) nuclei (case 95) (Lundsgaard¹⁵) as well as those of the vagus (Nemlicher¹⁶) also belong here. Disturbances of the bladder in the initial stages of the disease have been reported by Bugbee,¹⁷ and observed by us in two cases. All of these localized types of poliomyelitis were acute in character and were frequently fatal. None of our facial cases were fatal. One of our bladder cases died.

In a few instances the affection of the sympathetic nervous system has run a chronic course. Mendel¹⁸ described a peculiar, slowly increasing, bluish discoloration of the left leg in a young male. This extremity became cool and gradually an atrophy of thigh and calf, including the bones, developed. Hyp  sthesia, hyp  lgesia and hypothermia were noted. According to Mendel the clinical picture was caused by the involvement of the lateral horns of the spinal cord. Chronic progressive palsies of arms and legs associated with severe muscle atrophies have been seen by Comfort¹⁹. Particularly severe and remarkable were the disturbances in the observations of Sterling²⁰ and Foster Kennedy²¹. Sterling described palsies of the legs, of the muscles of the trunk and of the left facial nerve, acute bilateral panophthalmia and slowly progressing atrophy of the face involving its skin, muscles, bones and teeth. The author interprets his findings as a vegetative trophoneurosis. Foster Kennedy saw in a boy of 12 a sudden complete paralysis associated with a loss of bladder and rectal control. In the third week of the disease, lanugo hairs appeared all over the body. The patient recovered but the hair of the head stopped growing for several months.

The pathology of these chronic affections of the sympathetic system is but little known. Two possibilities have to be considered: (1) destruction of certain gray nuclei, and (2) changes in the paravertebral sympathetic trunks, or both.

Histologic changes in the sympathetic ganglia of the trunk and even in those of the intestines have been reported several times, but they are not convincing. Chronic lesions of the brain have been described in the litera-

ture in rare instances. Gross involvement of the brain has been described by Koenig,²² who reported hemiatrophy of the body and the extremities, which in some instances but not in all was associated with hemiatrophy of one of the hemispheres. We are able to confirm this finding. (See page 539.) The degeneration of the sympathetic nuclei in the medulla has been demonstrated by us in one chronic case. Bouttier and van Bogaert²³ reported diffuse degeneration of the spinal cord including the lateral horns, a finding similar to that described in the cord of our second chronic case.

The number of observations of chronic cases is, however, too small to warrant conclusions, but we have reason to believe that chronic changes of the sympathetic nervous system are more frequent than is generally known. This suggests the importance of investigating the possibility of preventing further development of the disease after the first signs of paralysis have developed. Our observations show that the poliomyelitis may very well produce severe and permanent destruction of the gray matter and that the disease is not always restricted to the spinal cord and the brain stem. The earlier in life the infection takes place the more damage it can do. In an infant with undeveloped and delicate nervous system the disease may interfere with further mental progress and produce idiocy or feeble-mindedness. The course of the disease in an infant is much more severe than it is in an older child.

Clinical, histological and etiological considerations have been used in order to work out a pathologico-anatomical classification. It has proved to be impossible to harmonize them. The etiology of poliomyelitis is not known and the histologic findings are shared by other types of encephalitis. These were the reasons which compelled H. Spatz²⁴ to propose a new classification based on the modus of the distribution.

Acute poliomyelitis is characterized by the involvement of the gray tissue of the spinal cord and brain stem. It is, therefore, a polioencephalitis and treatment must be directed at wide and scattered areas of infection. The distribution of the inflammation in the affected areas is spotty. This peculiar modus of distribution as well as the histologic response is shared by rabies, epidemic encephalitis, and the so-called Borna disease in horses. They constitute, therefore, one histologic group.

The similarity is limited to the acute forms of these diseases. The chronic conditions present entirely different pictures. Poliomyelitis destroys numerous gray nuclei in the spinal cord, in the medulla, the brain stem, and in wide areas of the gray matter—lesions which are very unusual in epidemic encephalitis. In the latter only the substantia nigra suffers a permanent degeneration and the resulting histologic picture differs fundamentally from that which we observed in the same region in our second chronic case. Chronic rabies is not known. The four diseases in question are four independent biological units produced by different, although in all instances ultramicroscopic viruses. Their therapy and their prophylaxis may be found to involve the same principles.

Different views have been advanced for the explanation of the peculiar distribution of the disease in the central nervous system. Spatz is of the opinion that the virus may reach the brain by way of the spinal fluid because the basal parts of the brain and its inner surfaces, as for example the walls of the third and the floor of the fourth ventricle, which are exposed to the spinal fluid, are particularly affected. He thinks that the virus travels through the peripheral nerves and reaches the spinal fluid in this way. This view may seem to be confirmed by experimental transmission of the virus through the ischiatic nerve or the cervical ganglia (Marinesco,²⁵ Hurst²⁶). Such an assumption, we think, is not tenable because typical infection may be produced by intracerebral injection without involving the spinal fluid.

Jungeblut and Spring²⁷ separated the lower part of the spinal cord in monkeys and closed the dura so that the spinal fluid passage remained free. An intracerebral inoculation produced a typical poliomyelitis in the animal but the infection did not pass the lesion. The virus traveled, therefore, through the nervous tissue itself, and not by way of the spinal fluid. This may lend further support to our feeling that intraspinal serum is unnecessary.

The pathology of the body organs in poliomyelitis is unimportant. The changes in the lymph glands as described by Flexner, Peabody and Draper,²⁸ 20 years ago, and by us, are characteristic of status thymico-lymphaticus. They are not peculiar to poliomyelitis. Catarrhal inflammation of the intestinal mucosa and of the lymphoid structures is not uncommon in other infectious diseases in childhood. It seems to us that the somewhat revolutionary view of Burrows, who believes that poliomyelitis infects first the lymphatic structures and only secondarily and in rare instances the nervous system, is rather speculative. Cowie and Lowenberg* have noted these general lymphoid changes in experimental poliomyelitis in monkeys inoculated intracerebrally.

From the standpoint of symptomatology, there is abundant evidence of central nervous system involvement in a very large percentage, if not in all, of the cases which do not go on to the stage of paralysis. There seems to be evidence of a systemic stage of this disease prior to involvement of the nervous system, as there also is in epidemic meningitis. This favors the opinion that the virus is probably carried to the central nervous system by way of the blood stream and encourages therapeutic effort via this route, although it is well known that the virus may travel along the nerve sheath, as has been accomplished experimentally. Dr. Flexner's well known experiments on monkeys show that the disease virus may travel through the nose directly along the olfactory nerves, and there is rather convincing evidence that the virus enters the body through the nasal passages in man. We have not been able to demonstrate changes in the olfactory

* Unpublished records

nerves We have seen involvement of the cranial nerves after intracerebral injection of poliomyelitis virus in monkeys

SUMMARY

In the four cases of acute poliomyelitis that came to autopsy, there was an acute inflammation in the spinal cord and brain stem in all and in the gray matter of the brain in one In one case the spinal cord alone was available for study

In the spinal cord, anterior, posterior, and lateral horns were affected and the greater part of their parenchyma was destroyed Neuronophagia was very frequent and the glia response was very active The blood vessel system of the cord was severely involved

In the medulla and brain stem numerous gray nuclei were affected in the same way as the gray matter of the spinal cord, the floor of the fourth ventricle being particularly involved There were numerous foci in the thalamus in two cases In these the inflammation was spotty, the foci being not always interconnected The gross pathology invariably showed extensive edema The progressive nature of the involvement was very apparent

Two chronic cases were also examined In one, there were numerous old degenerative foci in the gray matter of the spinal cord, in the substantia nigra, in the thalamus and in the gray matter of the brain In the other, large areas of the gray matter were destroyed and the medulla was hemiatrophic

The histologic picture varies in relation to the duration of the disease, it is dominated by the destruction of the parenchyma

Acute poliomyelitis shows a far-reaching conformity with acute epidemic encephalitis, rabies and Borna's disease of the horse Poliomyelitis affects the sympathetic system to a great extent It may cause idiocy if it occurs in infancy

CONCLUSIONS

1 We have recorded a study of 125 cases of epidemic poliomyelitis including data upon which our conclusions are based, 81 in the pre-paralytic stage, 44 in the paralytic stage The cases developed in the center of the epidemic There are also recorded a few chronic cases for purpose of discussion

2 Eighty of the pre-paralytic cases were under our complete control They received either convalescent serum, convalescent or adult whole blood transfusion, or a combination of these by the various routes of administration Seventy-seven, or 96 per cent, of these did not develop paralysis In those developing paralysis, recovery was complete No case shows any residual paralysis today

3 Twenty-seven of the paralyzed cases received immunotherapy as soon as they came under observation Of these 33½ per cent showed

definite improvement Three completely recovered, five died Seventeen paralyzed cases received no immunotherapy, 11.6 per cent improved, 86.64 per cent showed marked residual paralysis with little or no recovery

4 The progressive nature of the pathologic involvement of the central nervous system as observed clinically strongly suggests that immunotherapy and osmo-therapy should also be carried on in the early stages of the paralysis

5 Acute poliomyelitis involves the gray matter of the spinal cord, the nuclei of the brain stem, and the walls of the third ventricle It is, therefore, mainly an infection of the sympathetic nervous system The basal ganglia and the cortex are in some instances involved Scattered foci may be present in the white matter

6 Histologically the disease is characterized by the involvement of the neurons which are destroyed by the so-called process of neuronophagia

7 The inflammatory edema which is present in all acute cases must be regarded as an important factor in therapy and must be relieved

8 Epidemic poliomyelitis is a non-purulent type of inflammation It is one of a biologic group of diseases comprising rabies, epidemic encephalitis, and Borna's disease of horses

9 Histologic examination of chronic cases shows that in some instances the infection involves the entire cortex and interferes with the further development of the nervous system, producing feeble-mindedness and idiocy

10 The importance of the involvement of some of the brain areas, for example, the substantia nigra, is not manifested clinically as is a similar involvement following epidemic encephalitis by the Parkinsonian syndrome

11 Clinico-pathologic data are given which should assist in determining the results of the therapeutic measures employed

12 Blood group may be an influencing factor in the severity of the disease Seventy-seven per cent of the pre-paralytic cases fell in Types IV and III, 58 per cent of the paralyzed cases fell in Types II and I

We wish to express our sincere appreciation of the devoted assistance during the epidemic of Dr Dorman E Lichty and Mr William Hicks of the Contagious Hospital Staff, Miss G Kleinheksel, supervising nurse, and Drs Norman Capener and Louis Yglesias of the Orthopaedic Staff

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VIRUS DISEASES OF ANIMALS TRANSMISSIBLE TO MAN*

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INFECTIONS or diseases of animals associated with or due to incitants generally designated as viruses, since 1892, have attracted more and more attention. In fact, these maladies, single or in epidemic distribution, have assumed an important position in the realm of the heterogeneous infection chains.

The insect-borne diseases, yellow fever, dengue, pappataci fever, Rift Valley fever, etc., are caused by filterable incitants, which localize and multiply in the poikilothermic hosts and, consequently, are classed with the heterogeneous infections. Between the causative agent of the disease and the poikilothermic host, a specific mutual relationship exists and the insect (mosquito) is not merely a vector or transmitter but a definite host. A well regulated cyclic organization continuously shifts the relative position of man and insect. As far as the available information indicates, the disease incitant is never transmitted from man to man nor is it spread from insect to insect. Doubtless the continuous change between vastly different hosts must be accompanied by alterations in the biologic activities of the virus of the disease concerning which very little is known. Of interest is the further observation that the vector is slightly, if at all, affected by the virus. For the preservation of the parasite, this behavior is of the greatest importance. Should the vector succumb to the disease incitant or should the desire to suck blood disappear, then the transmission to man would cease and the chain would be regularly broken in the insect. In due course, the disease would become rarer and finally disappear entirely.

There is a second and decidedly larger group of infectious diseases, which may be conveyed from warm blooded animals either by the percutaneous, the alimentary or the permucosal routes to man. This group comprises virus infections, which are quite variable with respect to their localization, portal of entry and mode of transmission. Some of the incitants responsible for the diseases of this group possess a broad pathogenicity range, they are capable of infecting, in nature and experimentally, a great many hosts. Thus in nature, rabies is confined to a comparatively small number of species, dogs, cats, coyotes, foxes, wolves, jackals, horses, cattle, pigs, deer and moose, but artificial transmission is possible among a wide range of animals. In fact it may be assumed that no mammal or even bird is insusceptible. As a rule, the infection chains are broken following the first transmission to man. The restricted mode of natural transmission—percutaneous introduction of the virus through a bite wound as in rabies

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—is in part responsible for this behavior. A change of host, as for example a transfer to man, will sooner or later lead to a blind ending of the chain. A continuous passage in the animal host is obviously an absolute necessity. In some of the infections in man the clinical and anatomical characteristics are identical with those of the disease in animals. The neurotropism of the rabies and louping-ill virus is fully preserved. On the other hand, pulmonary manifestations are rarely seen in psittacine birds suffering from psittacosis, while they are the prominent symptom in the clinically recognized human infections with this particular virus.

Although it is the purpose of this paper to outline the effects of certain viruses, it may be permissible to inquire quite briefly into their nature. By usage, the term filterable virus is applied to a noxious agent or poison susceptible of being passed through a diatomaceous earth or kaolin filter impervious to ordinary bacteria. To a certain extent, this term is misleading since bacteria and spirochetes have been found capable of penetrating such filters, and a few incitants and the diseases caused by them have been placed with the filterable viruses even though they have not been shown to be filterable or only pass the filters with difficulty (rabies). The numerous painstaking studies of recent years have shown that many of the viruses are not merely enzymes or transmissible mutagens as was originally intimated by Beijerinck's description of the tobacco mosaic disease as a *contagium vivum fluidum*. In fact the evidence secured by special staining procedures (Borrel, Paschen, Goodpasture and Woodruff, Cowdry and others), dark field-ultraviolet microphotography (Barnard), differential centrifugalization (Bechhold and Schlesinger, Eagles and Ledingham, Bedson), ultrafiltration (Bechhold, Krueger, Elford), immunity reactions (Smith, Ledingham, Andrewes) and photodynamic inactivation (Perdrau and others) indicates that the viruses are, in all probability, living infectious, biologically defined particles capable of reproducing themselves true to type. Their sizes vary from 10 to 170 $\mu\mu$. They are obligate cellular parasites but thus far no one has succeeded in growing them on lifeless media. Since they cannot regenerate in the absence of living cells, their existence is demonstrated by their activity in susceptible hosts. However, the immunity reactions, which are employed, reveal a remarkable relationship between bacteria and viruses. Antigenically different types of viruses may incite identical symptoms (several viruses are capable of producing encephalomyelitis). Further, the corpuscular infectious particles are specifically agglutinated by antisera (vacinia) or the heated precipitable virus substance behaves like a hapten and incites skin reactions in the vaccinated human beings. In time these observations may be of aid in the preventive and curative aspects of the diseases caused by viruses but for the present the existence of such an agent is demonstrated by its activity in the natural and experimental host, in filtrates of tissues and in tissue cultures. The transmissible agents, in all probability animate in nature, are, therefore, judged by their activities and not by their morphologic or biochemical behavior.

Turning now to a consideration of the animal diseases caused by viruses transmissible to man, it may be profitable to confine the review to certain recent observations on rabies, Rift Valley fever and louping-ill, then to consider the problems regarding the possible transfer of foot and mouth disease, distemper and equine pernicious anemia to man and finally to discuss the psittacosis problem in the light of unpublished data collected in California

RABIES

Although not a disease of any great consequence in the total mortality of animals and man, the fear inspiring character of the symptoms and its mode of transmission, so vividly described by Fracastorius (1546), continue to hold the imagination of the investigators. The study of the causative agent, the aberrant types of the viruses and the modifications of the Pasteurian treatment remain fascinating problems.

In the fall of 1931, I received from Professor Rosenbusch of Buenos Aires a sample of a glycerinated brain specimen of a rabbit, which had been injected with nerve tissues of a cow dead from "Mal de Caderas." According to the accompanying letter, a comparative test with the rabies virus was suggested. The specimen was inoculated into rabbits and found to behave like a rabies virus, typical Negri bodies were readily demonstrated in the hippocampus. Shortly afterwards, a communication was received from Dr J L Pawan of Trinidad, who desired reprints and information concerning botulism in cattle. From a reprint of an article by Hurst and Pawan which was enclosed, it was noted that an epidemic affecting man and beast had appeared in Trinidad, and although the veterinary experts had diagnosed the disease in cattle as botulism, the evidence strongly pointed in the direction of a specific encephalomyelitis. Thus, an analysis of the relationship between the South American cattle and horse disease and the epidemic in Trinidad appeared desirable. Quite briefly, the facts established to date are as follows:

Since 1914, no case of rabies has been recognized in Trinidad, an island on which the strictest quarantine laws against rabies are in force. However, in 1929, cases among the human population simulating acute poliomyelitis made their appearance. Mainly children of school age were affected, and the 20 cases, which occurred in 1931, all ended fatally. The symptoms were those of paresis of the limbs, bowels and bladder, loss of sensation in the limbs and abdomen. A fatal termination ensued after an average of 8.5 days. The paresis followed an ascending course. Portions of brains sent to the Lister Institute, London, and to the Rockefeller Institute at New York produced on monkeys a virus infection indistinguishable from rabies. Negri bodies "Innen Korperchen" were regularly demonstrated. In the dog, the manifestations of paralysis predominate, those of biting are absent. Cross-immunity tests showed that the fixed virus protected in a certain number of cases against the intracerebral inoculation of the Trinidad virus, while immunization with the Trinidad virus protected

to a much lesser degree against the fixed virus. Results of serum neutralization tests showed evidence of a similar cross-immunity. Neuropathological lesions agree well with those recorded in cases of paralytic rabies. The anterior and posterior horns are equally affected, thus differing from the picture in poliomyelitis.

The features of the cattle disease were salivation, paresis of the legs, and a fatal termination after five or six days. A brain was sent to Hurst, who reported the presence of the rabies virus. The diagnosis of botulism had been based upon the clinical features of the cases, and upon the detection of the spores in the soil from the farms where cases had occurred. In two cows, the *Clostridium* was recovered from the liver and the spleen.

The epidemiological features of the human and cattle disease, both of which may be accepted as a form of rabies, are of greatest interest. In this connection, mention must be made of the reports by Haupt and Rehaag, who studied a cattle disease in Brazil as early as 1921, and of those of Costa and A. Costa and Rosenbusch in Argentina, and Migone in Paraguay during 1930 to 1933. These authors all agree that the disease is not contagious, has an incubation time of as long as two and one-half months, and is caused by the virus of rabies. Remlinger and Bailly, who tested the same virus as was sent to me, have definitely pronounced the Paraguayan virus to be a true rabies. On the other hand, Kraus and Duran, who experimented with the Trinidad and the South American virus, consider both to be varieties of the true rabies virus and designate it as *Paralyssa*.

Haupt and Rehaag were the first to establish the fact that the cattle had been bitten by vampire bats. In fact, the laboratory experiment of a bat biting a cow confirmed the supposition that these creatures were the vectors. In Trinidad, Dr. Pawan has demonstrated Negri bodies in the brain of a bat with unusual behavior. The occurrence of the cattle epidemics in the vicinity of wooded areas spoke in favor of a flying forest animal, the *vampire bat*—*Desmodus rufus*—and not the dog. A heifer, bitten 27 days before, died with symptoms of dumb rabies. The only human case at Trinidad, in which there was a history of a bite, occurred on July 6, 1931, and that was the bite of a bat. Symptoms developed on August 3, i.e. after 28 days. According to a more recent report, in three of the human cases mentioned by Hurst and Pawan, there was a definite history of a bite by a bat. Since this is not an uncommon occurrence in Trinidad, the investigators are of the opinion that final proof is lacking, although the evidence strongly incriminates the vampire bat as the transmitter of the disease. How the infection is spread among these mammals, and how they ever came in contact with a rabies virus remains a fascinating problem to be solved.

That rabies may show no tendency to spread among dogs is clearly shown by the observations made by du Toit in South Africa, who found that the yellow mongoose (*Cynictus pennicillata*) and the genet (*Genetta felina*), two wild carnivora, have caused human infections. The presence of rabies has been confirmed by an examination of the brain of a sick mon-

goose caught in the veldt How difficult the control of rabies may become, when the eradication of the transmitter is practically impossible, is well illustrated by these observations

The statistical reviews on antirabic treatment continue to emphasize the relatively low proportion of neuromuscular accidents following the use of dried or glycerinated cords However, the incidence is still much greater than after treatment by killed carbolyzed vaccines The subject of antirabic inoculation of dogs and domesticated animals with chloroform or phenol treated vaccines, or those fixed by passage from dog to dog has not crystallized into a unanimous verdict Although declared safe and efficient, the methods can serve only as an aid in the control of an outbreak of rabies In the United States, the elimination of the stray dog remains the major problem

RIFT VALLEY FEVER OR ENZOOTIC HEPATITIS

In 1931, Daubney, Hudson and Garnham described a virus disease affecting sheep, cattle and goats in the Rift Valley of the Kenya Colony Very young lambs are highly susceptible, and a mortality of over 95 per cent has been observed In ewes and cattle, the losses are relatively low Anatomically, characteristic lesions, in the form of a focal necrosis resembling that of yellow fever, are regularly encountered Infection through contact has not been observed, although the blood of the diseased animal readily conveys the malady by inoculation Preliminary experiments and field observations suggest an insect, probably *Taeniorhynchus brevipalpis* as the vector By moving the flocks of sheep from the mosquito belt to higher altitudes, the abortions and mortality in the ewes and lambs may be checked

Not the least important point connected with Rift Valley fever is the fact that the virus is pathogenic for man Four of the investigators who made the postmortems on the experimentally infected animals became infected In every case the attack was characterized by a very brief period of general malaise, the temperature rose to about 103° F, persisted for 12 to 36 hours, and was followed by headache and pains in or near the joints Every native engaged in the herding of sheep during the epidemic became ill for a period of four days In fact, close to 200 human cases of Rift Valley disease without any fatality are known to have occurred To prove the nature of the infection and to study its effect on a malarial infection, a man was injected with the diluted filtered virus On the third day, he developed a febrile reaction and felt ill Blood taken daily from the patient, infected lambs for a period of five days Clinically, Rift Valley fever in man resembles sand fly three-day fever It is differentiated from dengue fever by the fact that no rash, enlarged lymph-nodes or saddleback temperature chart accompanies the Rift Valley fever Subclinical infections have been recognized with the aid of the complement fixation test Incomplete evidence suggests the possibility that certain African rodents might serve as reservoirs

LOUPING-ILL

For more than a century, a disease of sheep on farms in certain areas of Scotland has been discussed and attempts have been made to determine its etiology. Early in 1929, Pool, Brownlee and Wilson succeeded in experimentally reproducing the condition in sheep and pigs by inoculations of portions of the central nervous system from diseased animals. The infective agent, which is filterable, was also found occasionally in the blood.

Subsequently, it was shown by Gordon, Brownlee, Wilson and McLeod that the ticks (*Ixodes ricinus*), which transmit the virus, also harbor another infective agent which causes a febrile disease in sheep. However, the most important discovery was made by Alston and Gibson, who transmitted the virus to mice by intracerebral injections. Thus a means was made practicable for a more extended use of this virus for laboratory studies.

In this connection it is worth remembering that the investigators emphasized the high infectivity of the virus. Contact of uninoculated with infected mice resulted in cage transmissions. This infectiousness has now resulted in laboratory transmission to man. Rivers has recently studied such cases by neutralization tests and has shown that persons who have had intimate contact with the louping-ill virus either develop a definite encephalitis, an influenza-like disease, or pass through a cryptic infection. The literature reports no spontaneous cases of louping-ill among men in the regions in which the disease is common in sheep. These laboratory observations will doubtless lead to further inquiries.

FOOT AND MOUTH DISEASE

The transmission of the virus to man must be considered as established, but its occurrence is quite rare. Despite numerous reports in the literature, undoubted cases characterized by an abrupt onset with fever, followed shortly by a vesicular eruption on the lips and mouth, the palms, soles and about the nails, and prompt recovery within two to four days, are few. Since a differential diagnosis cannot be made on clinical grounds, the reports of many exanthemata diagnosed as foot and mouth disease, without an infection or cross-immunity tests, are of little value. The susceptibility of man must be remarkably low, or otherwise it would be impossible to explain the absence of human infections following the use of small-pox vaccine contaminated with the foot and mouth disease virus. Thorshaug and Magnusson from Norway, and Motas from Rumania report such observations. The vaccine contained the foot and mouth disease virus in a highly virulent form and, when transferred to cattle and hogs, induced fatal infections. Equally convincing are the reports that only two proved human infections originated in the Institutes specially devoted to a study of the disease. To date, the number of human cases of foot and mouth disease, proved by transfer of the bleb content to susceptible animals, is, according to Trautwein, three (Pancera, Gerlach and Trautwein). The illness of a 25

year old caretaker, who accidentally cut his index finger on the right hand while infecting cattle with the foot and mouth disease virus, is particularly instructive. Two days after the accident, a small, burning bleb developed at the site of the already healed wound. Within two days, a multiple eruption appeared on both hands and feet. There was no rise in temperature nor general malaise. Within six days the blebs began to dry and about the sixteenth day after the onset, the crusts had fallen off. The contents of the blebs were tested on guinea pigs and a young pig. A type "B" foot and mouth disease virus was demonstrated. The blood of the convalescent contained neutralizing antibodies against the virus type "B," but not against type "A" or "C." Thus far, transmission from man to man has not been demonstrated, the infection chain is obviously broken.

INFECTIOUS ANEMIA OF HORSES

The transmissibility of the virus of infectious anemia of horses to man is of twofold interest. Although the only two human cases reported and proved refer to a German and a Dutch veterinarian, who both had intimate contact with diseased animals, it must be remembered that the virus may persist in the blood and tissues of horses for years and the affected animal may not appear anemic or sick. Since horses are used for the production of antisera for human use and since Koch has proved the contamination of sera with infectious anemia virus, it behooves the manufacturers of biologic products to select horses from areas in which swamp-fever has not been observed. The symptoms of one of the veterinarians, who had eaten infected horse flesh and had accidentally injured himself with an inoculation needle, consisted of headache, severe enteritis with blood in the stools, general weakness, emaciation, general pallor of the face and mucous membrane, and fever varying from 39 to 40° C. On two occasions, over a period of three years, the blood or the serum of the patient infected several horses after an incubation of from 26 to 39 days. Passage of the infective agent from horse to horse is readily accomplished. Thus it is conclusively proved that the virus of equine infectious anemia persisted in the body of a human being for at least three years. Another veterinarian suffered from severe anemia, his blood fatally infected three horses. These observations should be kept in mind and, particularly in the regions in which swamp-fever of horses is still prevalent (North Dakota, Nevada, Arkansas, Louisiana, Wyoming and Mississippi Valley), it would be desirable to test the blood of patients with obscure anemias by inoculating it into horses.

DOG DISTEMPER

Dog distemper is a disease which can be transmitted to comparatively few animals. Until Nicolle experimentally inoculated a human being with the filtered virus and proved, by reverse injection of the man's blood, the persistence of the disease agent in the body without producing clinical manifestations, man was considered insusceptible. Is the explanation of Nicolle

correct? Did distemper originate as a disease of man which gradually, through hereditary transmission of a resistance, lost its pathogenic properties for man, only to be transferred to his intimate associate, the dog? Is it not unlikely that certain respiratory infections in man are due to distemper? What is the significance of the recent findings that human influenza may be transferred to ferrets, the most susceptible animals for canine distemper? One awaits with interest further studies which may deal with the solution of these intriguing questions

The various pock diseases as virus infections should be considered under the general heading of this paper. Suffice it to recall that small-pox and all the animal poxes, except fowl-pox, are very closely related. In fact, it is probably correct to accept them as identical, and the variations which have been observed as merely adaptations to the particular animal with which they are associated. Each will, by passage through the calf, revert to the primal type, the cow-pox or vaccinia. The latter, as everybody knows, is readily transmissible to man, particularly through hands of milkers.

PSITTACOSIS

In recent years a virus infection of birds, readily conferrable to man, has assumed a wide distribution in the United States. This disease is known as *parrot fever* or *psittacosis*.

The single and group infections, which followed the exposure to South American and African parrots previous to 1929, attracted little attention. As a part of the great pandemic which followed the distribution of diseased parrots from Argentina and Brazil, an extensive outbreak of psittacosis made its appearance in November 1929. Armstrong placed on record 74 foci of infection which gave rise to 169 cases with 33 deaths from November 23, 1929 to May 7, 1930. Today it is fully realized that birds other than South American parrots were involved in the epidemic of 1929 and 1930. In fact since December 1931, it is definitely proved that psittacosis is a common infection in the breeding establishments of California. The commercial distributions of shell parrakeets (*Melopsittacus undulatus*) throughout the United States has resulted in at least 156 human infections and a mortality of 30, or 19.2 per cent. Until the avian disease has been eradicated, it is not unlikely that physicians will have an opportunity to encounter this disease. A somewhat detailed review of the present day knowledge appears justified.

The Infective Agent During the pandemic of 1929-1930 the virus character of the psittacosis disease agent was established by independent workers in England, Germany, the United States and France. Of particular importance was the discovery by Krumwiede, McGrath and Oldenbusch that the virus is readily transmitted to mice. The bacillus or *Salmonella psittacosis* has not been found in the course of the various studies conducted during recent years. In fact the extensive studies by Meyer and Eddie on several hundreds of infected shell parrakeets, and on the sputums

and organs of patients have proved the filterability of the disease incitant responsible for psittacosis. The virus is readily transmissible to white mice and various species of birds, in particular ricebirds and canaries. The fairly characteristic lesions produced in these animals are, as a rule, sterile but on microscopic examination reveal minute, Gram-negative ovoid or spherical bodies arranged in pairs and clusters. These corpuscular elements described independently by Levinthal, Cole, and Lillie are known as the L C L bodies or "*Rickettsia psittaci*". Their constant presence in definitely virulent material from different sources and the fact that filters with a pore width of less than 1.9μ usually retain the virus and thus indirectly define the particle size of the L C L bodies are facts in favor of the interpretation of the minute corpuscular elements as the infectious agent of psittacosis. In the diagnosis of parrot fever the L C L bodies possess the same value as Negri bodies in rabies. The virus is quite resistant to glycerine and under certain conditions to desiccation. However, it is readily destroyed by heat. In general, a strain of virus isolated from a parrakeet or a sputum may be passaged every six days. There is a tendency for certain strains to increase in virulence by passage in mice, but the virus does not become "fixed".

Birds Susceptible It is now fully appreciated that not only parrots and parrakeets are susceptible to psittacosis but that the canary (*Serinus canaria*), bullfinch (*Pyrrhula vulgaris*), nonpareil (*Cyanospiza cyris*), Java sparrow (*Padda oryzivora*), cockateel (*Leptolophus hollandicus* Kerr), Bengalese (*Uroloncha acuticauda*), Pekin robin (*Liothrix luteus*) and even the common fowl (*Gallus gallus*) may contract the infection by exposure. Recent observations leave no doubt that parrotlets (*Psittacula conspicillata* and *Psittacula spengeli*) and conures (*Eupsittula pertinax*) imported from Colombia and the native shell parrakeet or budgerigar from Australia may harbor the virus in the spleen and liver.

Disease in Parrakeets Shortly after the discovery of human psittacosis traced to California bred and raised shell parrakeets, a survey of the responsible aviaries was instituted. Visibly sick but mostly clinically healthy birds were autopsied and their organs, mostly spleens and livers, were tested for virus by intraperitoneal injections of mice. In acutely diseased birds the autopsy findings are as follows: A few drops of mucus on the ceres (nasal openings), a clean or soiled anus, thin, atrophic pectoral muscles, a large, heavy and tough, slightly saffron to ochre colored liver, occasionally (in about 10 per cent) studded with fresh or partially healed necroses and infarcts, slightly enlarged and congested spleen, rarely a few consolidated patches in the lower portions of one or both lobes of the lungs. The virus is readily demonstrated in the blood, brain and parenchymatous organs but not always in the nasal mucosa or content of the cloaca. The majority of birds examined, over 5,000, were the visibly healthy, well nourished shell parrakeets which had been chloroformed. The autopsy findings were essentially negative with the exception of a slightly or definitely enlarged spleen.

which quite regularly contains the virus. The degree of latent psittacosis in shell parakeets may be readily predicted by the percentage of spleens exceeding in diameter the normal average of 1 to 2 mm. Aside from the spleen and liver, the virus may be found in the ovaries and even the eggs. It is, therefore, not unlikely that the psittacosis virus may be transmitted congenitally.

Fifty-four, or 52 per cent, of 104 aviaries on which tests were made housed budgerigars with latent psittacosis. The percentage of virus carrying birds varied from 10 to 90 per cent. The virus leaves the body of the parakeet (or other birds) by way of the cloaca and the nasal mucus. The cloacal content is very rich in virus when the birds exhibit signs of diarrhea or polyuria. In the course of these tests on the elimination of the virus it was found that the livers and spleens may be non-infectious, while the nasal mucosa may produce typical psittacosis lesions in mice. Obviously, recovered birds may harbor the virus in the nose for an indefinite period. The infectiousness of a parakeet with psittacosis may be readily determined by placing in the same cage a pair of highly susceptible Java ricebirds.

Observations extending for several years have shown that avian psittacosis passes through an aviary about as follows. Many of the immature shell parakeets contract the infection early in life, the disease is rarely fatal. Within one and a half to five months the birds may recover completely and possess a sterile immunity. The recovery from the infection may be indicated by an enlarged spleen. Young parakeets may succumb to a relapse when transported in crowded cages or transferred into a cold climate. They are usually shedders of the virus and they may not only infect cage mates but human beings as well. Mature birds, eight months or older, are much more resistant and are seldom, if at all, involved in human outbreaks. Some may acquire a symptomless infection when exposed to shedding birds while others are entirely non-susceptible. The nature of this resistance is as yet unknown, it may be the result of a silent infection, or the result of a hereditary or maturation immunity. As far as preliminary studies indicate, the resistance is not associated with neutralizing humoral antibodies. Although the number of virus carrying birds and the danger of transmission of the infective agent to man progressively decrease with the age of the birds, it must always be remembered that the *incubation time* or the period which elapses between the injection of a shell parakeet with virus or the exposure to carrier birds may be from 41 to 106 days. A small percentage of the old breeding birds, cocks and hens, continue to harbor the virus and thus maintain the disease in the aviary. While the breeding operations are discontinued, deaths from psittacosis may entirely cease, but as soon as they are resumed, the malady may reappear and spread among the young birds.

Human Psittacosis In table 1 are presented the single cases or house epidemics which have been observed in the United States and Canada since 1929. One hundred and fifty cases had direct or indirect contact with diseased shell parakeets either in California or in other parts of the United

States and Canada to which this species of bird had been shipped During the same period infections, due to exposure to parakeets from Cuba, the "Orient," Yokohama and Holland, have been recorded In two, possibly three, cases the psittacosis infection was conveyed by canaries At least three, in all probability six, cases were secondary human to human transmissions

TABLE I

Psittacosis in the United States and Canada Due to California Parakeets and Canaries

| | | |
|--|----------------------------------|--|
| December 1929 | San Francisco, Calif | 1 case |
| January 1930 | Kansas City, Mo | 2 cases |
| March 1930 | Victoria, B C | 1 case |
| February 1931 | Milwaukee, Wis | 1 fatal case |
| February 1931 | Mantowoc, Wis | 1 fatal case |
| October 1931 | Los Angeles, Calif | 1 case |
| November 1931 | New York, N Y | 3 cases with 1 death |
| November 1931 | Los Angeles, Calif | 1 case |
| November 1931 | Portland, Ore | 2 cases, 5 suspects, 2 deaths |
| December 1931 | California | 13 cases with 6 deaths |
| January 1, 1932 to December 31, 1932 | California | 39 cases with 4 deaths 2 cases due to contact with canaries |
| January 1932 | Klamath Falls, Ore | 1 case |
| May 1932 | Chicago, Ill | 1 fatal case |
| July 1932 | Chicago, Ill | 3 cases with 1 death |
| August 1932 | Coloma, Mich | 1 fatal case |
| September 1932 | Several Counties in Minnesota | 19 cases, 8 suspects, 1 death |
| October 1932 | Boise, Idaho | 1 case |
| October 1932 | Malden, Mass | 2 cases with 1 death |
| October 1932 | Troy, N Y | 2 cases |
| October 1932 | Madison, Wis | 12 cases |
| October 1932 | Chicago, Ill | 1 case |
| January 1933 to December 1933 | California | 10 cases with 4 deaths |
| May 1933 | Sioux Falls, S D | 1 case |
| July 1933 | New York, N Y | 1 case |
| September 1933 | Minnesota | 1 case |
| October 1933 | Connecticut | 2 cases with 1 death |
| January 1934 | New York, N Y | 1 fatal case |
| February-March 1934 | Pittsburgh, Pa | 6 (5) fatal cases (?) |
| | Total | 130 cases 13 suspects and 30 deaths or a mortality of 19 per cent |

Cases Due to Parakeets from

| | | |
|----------------------------|----------------|--------------------------|
| <i>Orient</i> | | |
| April 1930 | Vancouver, B C | 9 cases |
| <i>Yokohama</i> | | |
| June 1930 | New York, N Y | 1 case |
| <i>Cuba</i> | | |
| January 1931 | New York, N Y | 5 cases |
| <i>Holland and Germany</i> | | |
| February 1932 | New York, N Y | with 2 deaths 2 cases |

The clinical manifestations, which were recognized as early as 1879 as a definite entity, have repeated themselves with remarkable regularity and uniformity. The composite clinical picture, as seen in the 50 cases concerning which histories or personal observations are sufficiently complete for analysis, is as follows:

The incubation time, although in many instances difficult to establish, is definitely known for 15 cases and varied from seven to 14 days after initial contact. In three cases, a single exposure occurred and the incubation period was seven, eight and nine days respectively. In human to human transmission the interval between the onset of the illness and the discharge of the nurse was eight and 13 days respectively. Quite important is the observation that in a third case the transfer of the virus from a fatal infection in a woman to her nurse was 30 days after discharge from the case or 39 days after the last exposure to infected parakeets. According to the published records, this must be considered an exceptionally long incubation period. The average is 10 days. As a rule, two to three weeks (average 14 days), but in a few instances three to four months, may lapse between the acquisition of the birds to the onset of the first case in a household (Ellcott and Halliday).

The onset has been mostly acute with chilliness, malaise and generalized pains, perhaps epistaxis. Prostration became marked during the first week and loss of appetite was always present. A temperature from 101 to 103° F or above presented itself and at first aroused no anxiety. Toward the end of the first week, however, the disease became more severe. Vomiting and, in about 25 per cent of the cases, diarrhea have been reported. A slight but irritating cough was constantly present. The headache was more intense and the patient presented the picture of a severe illness, ate little, constantly demanded fluids and lost weight. Restlessness, depression, tremor and bad dreams were followed by stupor and delirium and other encephalitic symptoms. The tongue was invariably coated a dirty brown and signs of a pharyngitis have been noted regularly. Abdominal distention and constipation were seen, and in one or two cases roseolae appeared on the skin. The temperature maintained itself at a high level with slight morning remissions in the fatal cases or it was definitely remittent, yet the pulse showed only a slight increase and stayed at the beginning below 100. Auscultatory examination at the beginning of the second week revealed no definite signs. Later, crepitant râles which moved from one area to another, usually beginning in the left lower lobe, were established. In the few cases in which roentgen-ray pictures were taken, the peculiar homogeneous, slightly opaque density and contour, and migrating location of the pneumonic process suggested the diagnosis of psittacosis. A cough, increasing in severity, was always present in the severe cases but it was only in 65 per cent of the patients. The sputum was or perhaps rusty and later definitely purulent. Respiration and pulse were increased.

definite area. Cyanosis and terminal pulmonary edema were seen in seven to 23 days after the onset. That the patient suffered from a very severe disease was amply attested by the pallor of the face, herpes labialis, blood-shot eyes, the semicomatose state only interrupted by delirious mutterings, restlessness and even violent excitement. Provided the pulmonary process was not too extensive, the patient's temperature dropped by lysis between the second to the fourth week. Recovery has invariably been slow and every patient complained of weakness and unsteadiness of gait for many weeks, even months. Relapses have been rare. Thrombotic-embolic processes were seen in one, possibly in two cases. Complicating bronchopneumonic infections, but in particular cardiac and vasomotor weakness, were responsible for the high mortality. A leukopenia (5,000 and 5,200) was noted in two of the 10 patients examined, while a normal count or a leukocytosis (17,200) was determined in the remainder of the group. A marked shift in the neutrophils to the left was always present. Although in about 15 per cent of the cases, the clinical picture resembled that of typhoid fever, the spleen was not palpable and the liver descended only in one or two patients. Aside from the severe cases, mild even ambulatory cases in old and young people have been observed. In fact the clinical observations differ in no way from those recorded in connection with the exposure to parrots. No explanation can be offered for the noteworthy fact that the same degree of contact and the same virus may induce a disease of a varying degree of severity. It is not unlikely that the susceptibility of man is quite variable and that a fair percentage may be immune or pass readily through the disease in a latent and subclinical stage. Treatment of the cases has been symptomatic with particular attention to the heart. Dr James B. Luckie has used leukocytic extracts hypodermically or intramuscularly. In some of the cases observed in the East, convalescent serums have been administered. The impression was gained that the disease was less severe but relapses were not prevented. Since weakly active neutralizing antibodies have been demonstrated in the convalescent human sera and since in some of the English cases antimeningococci serum and typhoid vaccine produced good results, it is quite likely that any agent which irritates the reticulo-endothelial cells is worthy of trial. However, mercurochrome in one case doubtless accelerated the fatal outcome.

In isolated cases, exposure to sick or dead parrakeets may induce clinical manifestations which in any one patient or in any stage of the malady are insufficiently characteristic to enable the physician to make a diagnosis. Various serologic tests for the enteric (*Salmonella psittacosis*) or undulant fever group of bacteria have been invariably negative, and it was merely the history of contact with parrakeets which finally aroused suspicion and led to a definite diagnosis. It may, therefore, be safely recommended that until the sale of non-infected birds can be guaranteed, it is well to be biased and to suspect psittacosis whenever a patient has recently brought psittacine birds or canaries into his or her household and suffers from severe influenza,

complicated by a migrating pneumonia. However, it is imperative that this suspicion or clinical diagnosis be confirmed, even though present laboratory methods frequently decide merely in retrospect. A definite laboratory diagnosis is also desirable for epidemiologic reasons. The majority of bird breeders, pet-shop owners, lovers of birds and even veterinarians still doubt the existence of such a disease as psittacosis.

The presence of the virus in the blood streams of patients has been established by Bedson and Western and by Meyer and Eddie. It has, however, been of little diagnostic value. In 28 clinical cases examined, the citrated blood of three patients infected mice when the blood was collected on the first, second and fourth days but not on the ninth, sixteenth or seventeenth days of illness. Since most of the patients rarely call a physician before the fifth or sixth day after the onset or at a time when the virus circulates irregularly, the mouse inoculation test with blood has been discontinued in California. However, the examination of sputums, first introduced by Rivers and Berry, has proved valuable. Since December 1931, Meyer and Eddie have tested the extracted, unfiltered but centrifuged sputums of 29 patients. A total of 42 sputum specimens has been examined. The virus was conclusively demonstrated in the sputum of 11 patients collected on the fifth, sixth, seventh, tenth, twelfth, fourteenth, sixteenth, twenty-third and thirty-seventh days respectively after the onset. One patient furnished a positive sputum on the fifth and on the tenth days but a negative one on the sixteenth day, while in a fatal case the excretion was infectious on the fourteenth, nineteenth and twenty-third days of the disease. In still another, the virus was found in the sputum on the tenth and thirteenth days. Seven of the nine cases observed in California since January 1933 had the nature of the infection proved by positive sputum findings. The failures to find the virus may be ascribed to the improper collection of the specimens late in the course of the infection. Since the virus is eliminated, irregularly repeated examinations on 24 hour specimens should be made. Microscopically, the secretion shows, as a rule, a few neutrophils, lymphocytes and large alveolar epithelial cells. The autopsy material of six human cases revealed the virus in the lung, spleen and liver in three, while in the fourth, the spleen and liver were devoid of sufficient virus to infect mice. From two autopsies the organ specimens were sent in the same container, consequently, separate examinations could not be carried out.

Epidemiology As might be expected, over 70 per cent of the human cases in California and elsewhere have been caused by newly acquired shell parakeets. The majority of infections resulted from exposure to sick and, subsequently, dead budgerigars. These observations, together with the laboratory findings on the epidemic birds, indicate that the sick or dead parakeets are more dangerous, largely on account of the liberal elimination of the virus through the nasal mucus and the droppings. The pathways of transmission of psittacosis from birds to man are probably twofold: (a) direct contact through the handling of the corpse of a bird which had died

of the disease, by feathers or excreta, by nasal discharge and through bite wounds, (b) indirect by the aerogenic route

There is no doubt that the droppings and nasal discharges of the birds are readily scattered by the flying motions of the birds, which are easily agitated by the persons who handle or approach the cage. Air currents may disseminate the suspended virus particles. The environment of an infected group or of a single parakeet may, therefore, be charged with virus and becomes a menace to human beings who may inhale it. It is, however, still a matter of conjecture whether the psittacosis virus in the droppings will regularly withstand prolonged drying and thus become dangerous. Furthermore, the possibility of infection by ingestion should not be ignored. Careful experiments are needed before a definite opinion can be expressed as to the importance of one or the other route. The high infectivity of the dispersed psittacosis virus, which resembles that of small-pox or measles, is shown in the histories in which a very short exposure occurred in a pet-shop where diseased birds were kept. It is, therefore, fully proved that, contrary to the general belief among the laity, actual contact or possession of parakeets is not necessary. A brief visit in a room with birds or sojourn in a baggage car transporting birds may be followed by disease in the susceptible.

Case to case infections, already reported as early as 1898 by Leichtenstern and subsequently by Hegler, Hatfield, Sturdee and Scott, Armstrong, Ellicott and Halliday, and others, have been definitely proved in three cases in the California series. The evidence at hand strongly suggests a human to human transmission in three additional cases.

An interesting characteristic of psittacosis outbreaks is the occurrence in house epidemics. In three instances, man and wife, in a fourth, brother and sister, and in the fifth, several guests of the same household contracted psittacosis. This feature of multiple cases in the same house may be of diagnostic value (Barros).

In this connection consideration should be given to the *attack rates* in general. It is well known that heavy exposure, as for example, the employees in pet-shops or visitors in rural households, may be between 65 to 100 per cent. In occasional exposures the rate may be as low as 6 per cent. At the beginning of the investigation in California the bird breeders and the persons associated with the bird fancying trade pointed to their apparent immunity and, consequently, denied the existence of psittacosis. Logically, it was reasoned that a disease, alleged to be derived from parakeets, would primarily attack those who are constantly in contact with these birds. Some credence was given to these arguments until systematic surveys not only proved the existence of psittacosis in aviary owners by laboratory tests, but revealed the fact that a history of a "severe attack of influenza with pneumonia" in bird breeders was occasionally elicited. It is naturally a matter of conjecture whether these "influenzal attacks" were true psittacosis or not. The fact remains that, of the 66 cases of psittacosis infections reported in California, 25 or 38 per cent were in owners of large or small parakeet aviaries or in members of their families.

The great epidemics of the past, in particular the pandemic of 1929–1930, occurred during the winter months. Epidemiologists, therefore, have expressed the opinion that the prevailing disposition to respiratory infections, during the colder months of the year, favored the spread of psittacosis. There is little support to this interpretation in the California data as shown in chart 1. It is true that in December 1931 and in January and

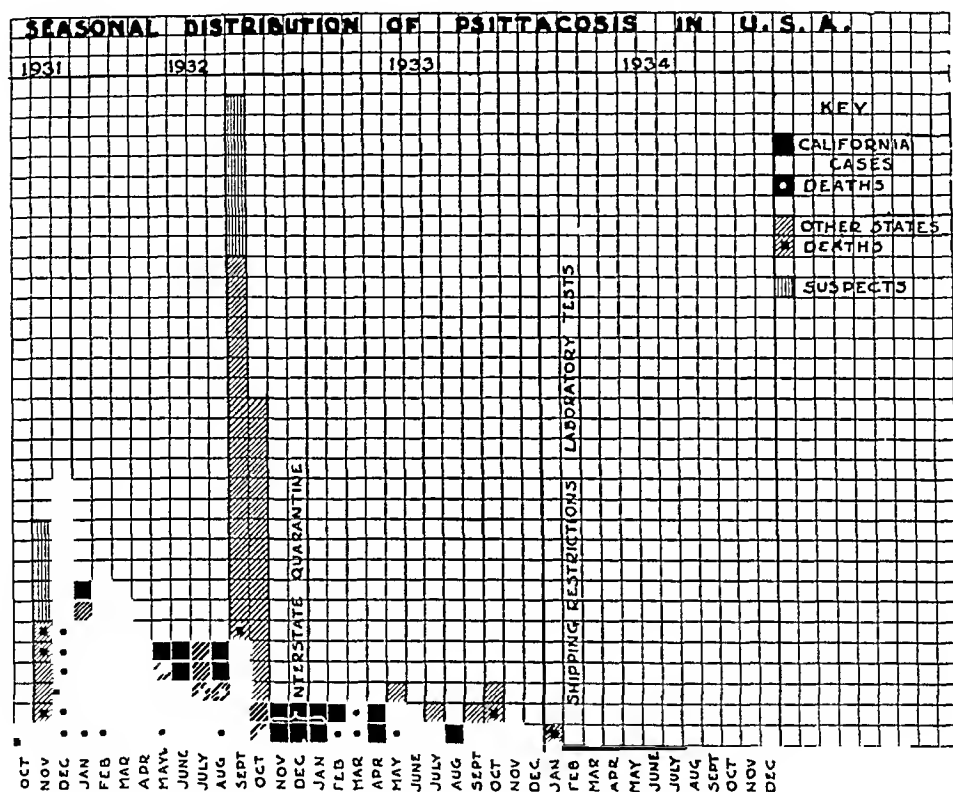


CHART 1

February 1932, many new cases were recognized. However, it must be appreciated that shortly before these dates, a great many infected young birds were freely distributed for the Christmas holidays and a vigorous investigative campaign assisted in the location of cases, which would otherwise have been missed. By contrast, no cases were seen or reported during the very cold months of November or December 1932, or January 1933, when a complete inter- and intrastate quarantine paralyzed the traffic of parrakeets. There is, therefore, no support to the contention that the cold winter of 1931–1932 precipitated the outbreak. Scattered cases reappeared when the handling and shipping of birds were resumed. Many cases were seen in September and October and severe psittacosis is not uncommon in midsummer. It may, therefore, be concluded that the seasonal fluctuations are only influenced by the prevalence of infected birds. Usually, in the fall and early winter, immature carriers, sick birds and their mates, which cannot resist the vigors of transportation, reach their destination and are readily

case, usually revealed one or two other milder cases, and thus helped to ameliorate the staggering mortality rate

Protective Measures Theoretically, psittacosis is a disease which could be easily controlled provided the public would appreciate the possible danger inherent in contact with birds, particularly of unknown origin. However, the love for pets so deeply rooted in human nature cannot be changed (Hasseltine). After nearly two years of struggle to accomplish some degree of protection by means of restrictive measures such as embargo and quarantine isolation, it becomes apparent that only one course is left open, namely, the systematic examination of the parrakeets by autopsies and laboratory tests and the destruction of the bird population of the aviaries housing infected budgerigars. This programme is now in process of execution. Time alone will tell whether it is possible to create breeding establishments free from psittacosis. Bird breeders and pet-shop owners, whose parrakeets have caused sickness and death, still declare in 1934 that psittacosis is an imaginary malady and the publicity a hysterical propaganda to injure their business.

In conclusion, it should be stated that the few examples were merely chosen to illustrate the complexities of a relatively new field of medicine. As a reservoir of human virus disease, the animal kingdom offers many intriguing possibilities and surprises.

UNDULANT FEVER¹

By JOSEPH L. MILLER, M D, F A C P, *Chicago, Illinois*

WHILE we are not justified in calling undulant fever a new disease in this country, there is no doubt that of late there has been a great increase in its incidence. This I believe can be explained only in part by new interest in and consequent recognition of this disease. The character of the fever curve in many cases is so unlike that of any known fever, that it should have attracted the attention of physicians in the past.

A few imported cases were reported as early as 1897. C. F. Craig in 1904 reported the first recognized case acquired in this country. In 1926 46 cases were reported in the United States and in 1932, 1505 cases. One-third of all those reported in 1932 came from three states—California, Missouri, and New York.

The first appearance of this disease in epidemic form occurred in southwestern Texas. In 1913 it appeared in epidemic form in southern Arizona. Eight years elapsed before another epidemic was observed, this occurred in Phoenix, Arizona, in 1921. All of these arose from infected goats. Because it was restricted largely to goatherds and those who handled the goats during the kidding season, it is probable that contact, rather than milk, was responsible. It is reported that 25 years previous to the Texas epidemic there was a peculiar epidemic fever which received the popular name of goat fever.

If other cases of fever resembling that seen in this disease were observed in this country, they have not been reported with sufficient accuracy to enable one to claim that they were cases of undulant fever.

This disease had long been present in epidemic form in the Island of Malta. Sir David Bruce (1886) who was assigned to determine the nature of this infection was able to obtain, in smears of organs obtained at autopsy, a microorganism which later proved to be the etiologic agent. It was not, however, until 20 years later that the goat was recognized as the host. This was a chance finding. Animal experimental work was planned and, as the goat was the most readily available animal, six of these were secured for this purpose. A preliminary blood examination was made and it was found that five of the six goats agglutinated the microorganism isolated by Bruce in high titre. B. F. L. Bang in Germany isolated a similar microorganism from aborting cows in 1897, but it was not until 1918 that its pathogenicity to man was recognized. In German literature Bang's name is attached to this disease. In 1914 J. Traum isolated a microorganism from pigs with epidemic abortion.

There has been, and still is, considerable confusion in nomenclature. Alice Evans demonstrated that the microorganisms isolated from these three

¹ Read at the Chicago meeting of the American College of Physicians April 20, 1934

sources were identical as far as could be determined by ordinary cultural methods. In this discussion, *Brucella melitensis* is used for the caprine, *Brucella abortus* for the bovine, and *Brucella suis* for the porcine strain. Huddleson¹ by using different dyes in the culture media was able to differentiate these three strains. It might be mentioned that a microorganism similar in character has been isolated from horses, chickens, sheep, and, in one instance, from an aborting bitch.

The bovine strain is responsible for undulant fever in most city dwellers through the ingestion of infected milk. In packing house workers and among farmers, the *suis* variety is not infrequent, probably from contact infections. Hardy, Jordan, Boots, and Hardy² found the *Brucella suis* in 20 cultures from farmers, only one of whom had had close contact with hogs. They also obtained *suis* cultures in four farmers' wives. Hardy claims the *suis* variety may be found in cow's milk. He also states that it is much easier to obtain positive blood cultures in *suis* infections than in infections with *abortus*.

Considerable work has been done to determine the incidence of diseased cows, by the use of the agglutination test. Apparently, there is considerable difference of opinion as to what titre can be considered positive. Hardy considers a 1-80 titre as positive and a 1-40 as suspicious. When testing herds in Iowa he found, in 1300 cows tested, 26 per cent positive and 8 per cent doubtful. Dietrich and Bonyne³ reported 36.7 per cent of 3000 cows in Los Angeles as being positive. Dr. C. P. Fitch (chief of the University of Minnesota Farm at St. Paul, Minn.) has tested all herds in scattered townships in Minnesota on the basis that a titre of 1-250 is positive and 1-150 suspicious. He has reported that 5.8 per cent of the cows in these areas were positive and 5.9 per cent suspicious. In 123 blood cultures from infected animals, only four were positive. In some herds he found over 20 per cent of the cows positive and 12 per cent suspicious. Starr⁴ states that in the course of the two years, 1931-1932, 45,285 dairy cows were tested. Ten per cent were positive. In an abstract of his report, from which this information was obtained, no mention was made of the titre.

Fitch claims that at least 85 per cent of abortions in cows are due to the *B. abortus*. The disease, he believes, is spread by introducing a new infected cow into a herd. Between pregnancies the infection is apparently latent, but becomes active in the uterus during pregnancy and the cow aborts in the fifth to seventh month. As not all infected cows abort, absence of abortion is not evidence that the herd is free of infection. A bull may become infected from a cow and such infection is usually followed by orchitis.

The placenta and amniotic fluid are heavily infected and also the vaginal discharge which continues for about three weeks after abortion. It is Fitch's opinion that cows become infected from forage that has become contaminated by the amniotic fluid or vaginal discharge of diseased cows.

Calves nursing from infected mothers rarely show any evidence of infection, although the germs may be found in the feces. These discharges are probably another means of contaminating forage. It is the general opinion that the cow does not develop an immunity, that the disease is chronic with a latent period between pregnancies. Fitch states that in examining milk he has found that the gravity cream is most likely to contain the microorganism.

INCIDENCE IN MAN

Four years ago Dr. A. V. Hardy, under the auspices of the National Institute of Health, made a survey of the entire state of Iowa to determine the incidence of undulant fever. He found 375 active cases widely disseminated throughout the state. Iowa is an agricultural state and 42 per cent of the inhabitants live on farms. In 10 instances he found more than one case in a family. In one instance an entire family of nine were infected. Seventy-seven per cent of the cases were males and 44.7 per cent of these were farmers. Among the women infected, 66 per cent were in farmers' families. Packing house employees showed the highest incidence. In a group of 100 positives who had no direct contact with live stock or fresh meat, it was presumed that the infection was acquired from raw dairy products. The disease was practically equally distributed between the two sexes—51 per cent male and 49 per cent female. The high incidence of males among farmers speaks strongly for the fact that the infection is acquired by direct contact.

Carpenter and Boak⁵ determined that guinea pigs were easily infected by gently applying a culture on the bare skin at the base of the animal's ear. They found that infection with the porcine strain through this channel was more readily attained than with the bovine strain. When taken by mouth, the animal is more readily infected with the bovine strain. In the group where the infection took place, presumably by direct contact, 29 positive blood cultures were obtained and 24 of these were the suis strain. Attention has already been called to the greater ease with which blood cultures can be obtained in suis infection. From these observations, we may conclude that milk or the handling of raw meat is not the sole manner in which infection is transmitted.

Studies have been made to determine by the agglutination test the incidence of this disease in certain occupations. These results are of limited value because investigators have not been able to arrive at definite conclusions as to the minimum titre that may be called positive. If such a test is positive, it means only that the patient at some time has been infected.

Dible and Pownall⁶ made a study of the agglutination test in packing house employees working on sheep, pigs, and cattle. They considered a titre of 1-40 positive. They found the highest incidence in those working with cattle, second, sheep handlers, and the lowest incidence in those working with hogs. Consequently, this indicates that infection may come from contact with sheep.

Veterinarians frequently show a high incidence of positive tests. In the great majority of those with positive tests there is no history of illness. There is abundant evidence that the agglutination test may be positive in the absence of any previous clinical manifestations. Huddleson and Johnson⁷ tested 49 veterinarians. Of these, 57 per cent were positive and 26 per cent, in addition, had a positive agglutination in a titre of 1-100. Therefore, the total of positive or suspicious equals 83 per cent. Only three gave a definite previous history of undulant fever.

Thomsen⁸ made a complement fixation test on 65 veterinarians and found 84.6 per cent positive. In none of these was there a previous history of infections.

A group of 18 veterinary students was examined—all were negative. Five months after entering practice 83.3 per cent were positive. In 16 bacteriologists working with *Brucella* 63 per cent were positive. In a group of 29 farmers 39 per cent were positive. In a group of 20 butchers 20 per cent were positive. As the complement fixation test alone was used on all this group, it is unwise to compare the results with those obtained by the agglutination method.

There has been some suspicion that the test may be positive in patients with typhoid fever. Bayne-Jones⁹ made agglutination tests on 180 patients reported to have typhoid fever and all were negative.

There are a number of reports where all sera sent to municipal, state and private laboratories for Wassermann or agglutination tests have been tested by complement fixation or agglutination for evidence of *Brucella* infection.

Sasano, Caldwell, and Medlar¹⁰ examined 1000 specimens by complement fixation—4.9 per cent were strongly positive, 4.7 per cent were weakly positive. In the agglutination test 4.1 per cent were positive in a titre of 1-45 or higher and 3.6 per cent positive in a titre of 1-15. In the 49 who gave a strongly positive complement fixation test, 36 also gave a positive agglutination. Four sera that gave a positive agglutination test in 1-45 to 1-135 gave negative complement fixation tests. Only five sera came from patients with clinical undulant fever.

Ruth Gilbert and Marion Coleman, in the laboratory of the New York State Health Department, examined 848 sera submitted for Wassermanns—0.4 per cent gave agglutination in 1-80 or higher. In 1186 sera submitted for agglutination test for typhoid 5.9 per cent gave a positive agglutination with *Brucella*, indicating that undulant fever may be mistaken for typhoid. In 1186 sera submitted as possible undulant fever, 11.5 per cent were positive. Just how many in this group were proved to be undulant fever is not known.

Meyers¹¹ in Nebraska tested 1000 sera submitted for Wassermanns. Of these 4.3 per cent were positive.

Hardy in his monograph has a very interesting report on agglutination tests on sera from various sources. These specimens came from the Iowa

State Laboratory and included sera for Wassermann and Widal, also sera from tuberculosis sanatoria, Iowa packing house employees, apparently healthy veterinarians, and from the Chicago Board of Health Laboratory. The sera from Iowa, submitted for Wassermanns, showed 9 per cent positive in a 1-20 titre, the sera from Chicago showed 1.5 per cent positive—showing the higher incidence of positive sera in Iowa. In the specimens submitted for Widal from Iowa 4.4 per cent were positive in a dilution of 1-20, specimens from 85 veterinarians showed 7.5 per cent positive in a dilution of 1-20, and 4.2 per cent positive in a dilution of 1-40—again showing a higher incidence as a result of contact infection. Inmates of a tuberculosis sanatorium showed 3.1 per cent positive in 1-40 and 2.9 per cent positive in 1-160 or higher—this might be accounted for by milk from an infected herd. The consumption of an unusual amount of milk would also increase the probability of infection. There are other reports showing an increased incidence of positive agglutination tests in tuberculosis patients. In the sera from 150 healthy packing house employees, he found a definite increase in positive titres—26.4 per cent were positive in a titre of 1-20 or more, 18.4 per cent positive in a titre of 1-40 or more, 7.8 per cent positive in a titre of 1-320 or higher, 1.3 per cent positive in a titre of 1-2500. The frequency of positive tests in high titre in people probably infected, but without present or past clinical history of any infection, indicates the restricted value of the agglutination test in determining the presence of an active infection.

A most interesting observation has been reported by Dooley¹² namely, that during an epidemic many of those using the infected milk may show high agglutination titre without symptoms. His observation was made in an Eastern boys' school where raw milk, from a private herd, was used. In 1925 epidemic abortions appeared in the herd, 12 cows aborting. Following this, any boy who had fever was given an agglutination test and this test was also given to many boys without fever. All tests were negative up to November 22, 1930. On that date one boy developed undulant fever and shortly after this a second boy. Investigation showed that one cow aborted on November 13 and that her milk was not used until November 18. This cow and four others which showed positive agglutination tests were removed from the herd and all milk was pasteurized. Following this, all the boys (232) and 31 adults were tested for undulant fever by the agglutination test—109 or 41.3 per cent were positive. 62 in a titre of 1-10 to 1-40, 32 in a titre of 1-80 to 1-160, 6 in a titre of 1-320 to 1-640, 5 in a titre of 1-1280 to 1-2560, and 4 in a titre of 1-5120 to 1-12,000. None of these boys had fever or were ill. The highest point in agglutination titre in this group was reached in January and February and after this the titre gradually fell. Eleven of those boys who had a titre of 1-10 to 1-40 later developed acute fever, chicken-pox, pertussis, sore throat, or febrile reaction after protective inoculation to typhoid. This was followed by an immediate rise in the agglutination titre. In one case

it rose from 1-80 to 1-640 This observation is of interest in that it shows the effect of an infection or febrile reaction on the specific titre

We may draw the following conclusions from this observation

First Only 2 per cent of those infected had symptoms, the others were unaffected by the infection If this be true, generally not more than 2 per cent of infected individuals are ill

Second A later mild febrile reaction may greatly increase the agglutination titre and might mislead the clinician into making a diagnosis of active undulant fever

From a diagnostic standpoint, it is important to know how long a positive agglutination test may persist There are several observations on this point which indicate that within six months, in some cases, the titre may be negative In one series of 45 cases reported by Hardy, 30 were still positive in 1-40 after 12 months

ONSET AND SYMPTOMS

The incubation period varies from five to 15 days

I know of no other acute infection in which there may be such a variety of symptoms, nor one in which there is such extreme variation in intensity and duration The onset may be so mild, and the symptoms so insignificant, that the person is unaware that he has been ill On no other basis can we explain the positive agglutination in people exposed to infections, but without any history of illness The onset may be acute, with chill and those symptoms common to acute febrile diseases The high fever may continue with intermissions for many years The outstanding symptoms are a septic type of fever with frequently recurring chills and drenching sweats, especially at night Very frequently, in fact an almost constant symptom, is arthralgia which in some cases may lead the physician to suspect he is dealing with an acute arthritis Frequently there is abdominal distress usually recurrent in character, which may be mild or severe and often localized A considerable number of patients have been operated upon for appendicitis or cholecystitis

The type of fever is extremely variable except that it always shows considerable daily fluctuation The typical textbook wave-like undulating fever is not common When present, it may persist throughout the course of the disease or be present inconstantly Only rarely does the fever resemble typhoid, as the daily variation is more marked The high septic type of fever may suddenly drop to normal, may remain so for days or for weeks, and then abruptly (often with a chill) re-assume its former characteristics Not all patients, however, have this characteristic drop in temperature In four of the seven cases I have seen, such drops in temperature have been noted In one case, where the disease is now in its seventh year, the patient has had three cycles when the temperature disappeared for months In one of these cycles the patient was afebrile for six months and gained 20 pounds in weight The presence of this type of fever is not

observed in this country in any other disease and, when present, is of high diagnostic import. Rat-bite fever may be intermittent, but is quite different as it has one-day fever with three- to five-day afebrile periods.

Excessive sweats, without great impairment of the patient's appearance of well being, also are of diagnostic value. In the long continued cases the patients do not show the typhoid facies. It is true that they may lose in weight, but this is due to the high fever and consequent increased basal needs rather than to anorexia. Delirium is extremely rare, usually transitory and associated with hyperpyrexia. There may be high fever, but very moderate evidence of toxicity. The physical appearance of the patient may have high diagnostic significance.

Joint disturbance is another almost constant symptom. It has been present in all of my cases. There is subjective pain and tenderness, but no swelling in the mild cases. On the other hand, the joint manifestations may be so outstanding that they resemble those of acute rheumatic fever. If the patient has an afebrile period, the joint disturbance subsides in a large measure. In one of my cases the joint changes in the fingers had the characteristic spindle appearance seen in chronic rheumatoid arthritis and the condition had been so diagnosed. An intermission of the fever was followed by a disappearance of the joint swellings.

Suppuration of the costo-sternal and costo-chondral junction has been reported. Kulowski and Vinke¹³ reported as a complication a suppurative spondylitis. Feldman and Olson¹⁴ have observed similar changes in hogs affected with this disease and have obtained a pure culture of *Brucella* from the pus.

Gastrointestinal symptoms of a peculiar character may be present. Nausea may be a symptom in any severe infection and may be observed in patients ill with this disease. However, the symptom that has some diagnostic significance is pain, intermittent, usually somewhat localized, but not confined to any particular part of the abdomen. When the pain is present there is localized tenderness. It has been reported that this symptom is more frequently present early, but I have seen it present in a case where the disease was in its eleventh month. The presence of such a recurrent pain has diagnostic significance. Simpson and Bowers¹⁵ have reported a number of patients with unrecognized undulant fever who have been operated upon for appendicitis or cholecystitis. The true cause of this pain has not been explained. An initial diarrhea has been reported, whether or not this ever persists, I have not been able to determine.

A prolonged septic type of fever, often with intermissions, arthralgia, profuse sweating, and intermittent gastric distress—when all are present—make it highly probable that the patient has undulant fever, even in the absence of a positive agglutination. Various complications may appear in the course of the disease, such as mastitis, oophoritis, and orchitis. One case with liver abscess has been reported and several cases with acute cholecystitis.

The pulse usually varies directly with the temperature. The spleen is usually, but not always, palpable. A slight, circumscribed macular or papular eruption has been described. Acute endocarditis, due to the *Brucella*, has been reported. As a result of prolonged fever, myocardial changes may develop and become manifest in the form of acute dilatation. In one of my cases, the patient developed acute dilatation of the right heart after eleven months of fever, without any preceding exertion to explain it. She recovered and at present has a competent heart. This same patient had also a fibrinous pericarditis.

LABORATORY FINDINGS

There is the usual secondary anemia. The leukocytes may be normal, or slightly increased in number, or there may be a leukopenia. In one of the cases in my series, during an unusual hyperpyrexia, the leukocytes reached 33,000. Considerable stress has been laid on the relative or absolute decrease in the polymorphonuclear cells. In patients with moderate leukocytosis, the percentage of mononuclear cells may equal the polymorphonuclear. This finding is of value when present, but it is not constant. One patient in my series never showed these blood changes.

Blood cultures when positive establish the diagnosis. Unfortunately, positive cultures can be obtained in only about 25 per cent of cases. So important is a positive blood culture that if, in a clinically suspicious case, it is negative it should be repeated several times.

Agglutination Test In the absence of a typical clinical picture much stress has been placed upon the agglutination test. From observations recorded in this paper we can readily see the fallacy of accepting such a test as conclusive. The epidemic in the boys' school showed that those infected, but free from clinical manifestations, had a great increase in titre during a febrile reaction, due to any cause, which might lead a clinician to conclude that he was dealing with active undulant fever. Furthermore, it has been shown repeatedly that patients with this disease may have a positive blood culture and negative agglutination, or agglutination in very low titre. On the other hand, if we accept low titres as positive, we will find a considerable number of patients, especially in certain vocations, who as a result of a symptomless previous infection, will give agglutination in low titre. The lesson to be learned from this is not to accept a positive agglutination if the patient's symptoms are not in accord with this diagnosis. If the patient's condition resembles an undulant fever clinically, do not abandon your clinical diagnosis even when there is a negative agglutination test, but continue to get repeated agglutination tests and blood cultures. Two of the patients in my series (one in whom the disease has been present for six years, the other, in whom it has been present for 11 months) clinically were cases of typical undulant fever. Early repeated blood cultures and agglutination tests, made by highly competent laboratories, were negative. Finally, after repeated agglutination tests, one of

the patients showed positive in 1-160, but a week later the agglutination test was again negative. The other patient, after repeated negative tests was positive in 1-80, then again negative, and later again positive. This same phenomenon has been observed in the Widal test for typhoid. Another patient in my series showed the first positive agglutination test in the seventh week of the disease. It is obviously impossible to determine the minimum titre that may be pronounced positive.

It has been reported that the failure in the agglutination test might be due to the presence of different strains of *Brucella*. Hardy has checked up on this by using 46 strains, including both abortus and suis, and has found no variation in titre beyond the limits of experimental error. He occasionally found a recently isolated strain to be more resistant to agglutination, but this resistance disappeared after the fourth sub-culture. Marked zone phenomena have been observed. High titres may be positive with low titres negative.

Complement fixation test and intradermal tests are open to the same criticism and are, I believe, less dependable than the agglutination test.

The reduction in the ratio of the polymorphonuclear cells in the blood may be of great diagnostic value when positive, but of little value when negative.

DIAGNOSIS

No attempt will be made here to discuss differential diagnoses. This has already been well done by others. From my limited experience, I believe that the diagnosis may be more difficult than in any other acute infectious disease. The recognized cases probably constitute only a small percentage of the persons infected. I only wish to emphasize the importance of accurate bed-side observation, using the laboratory as an aid.

DURATION OF THE DISEASE

There is wide variation in the duration of the disease. The febrile period, in clinically recognized cases, may last only two or three weeks. In other cases the disease takes on a chronic form and continues for many years.

MORTALITY

The mortality, if we were able to diagnose sub-clinical cases, would be extremely low. In recognized cases it will average about 3 per cent.

THERAPY

Preventive methods are now limited largely to the elimination of infected cows and the pasteurization of milk. Pasteurization is effective when properly applied. There is still considerable difference of opinion in regard to the titre in cows that may be considered positive. Probably cows vary in this respect the same as man. If these two methods of pre-

vention were carried out efficiently, we would still have the problem of contact infection, the elimination of which offers apparently insurmountable difficulties

Experimental efforts to immunize cows against this disease have not been successful

Active Treatment Regarding active treatment one is inclined to believe with Hardy that "We find no record of a properly controlled systematic investigation in therapy" For this reason different forms of treatment will not be discussed in detail The not infrequent sudden termination of the disease may readily deceive the therapist

Vaccine therapy in cows, according to Fitch, is of no value In man specific vaccine therapy is at present at a very low ebb When vaccines are given in large doses subcutaneously, sufficient to cause a marked rise in temperature, or intravenously, with consequent febrile reaction, if results are obtained they are probably due to foreign protein therapy rather than the result of a specific vaccine

Chemotherapy has failed

Experimental work with serum therapy in guinea pigs has at best been only moderately successful (See report of work of Gwatkin¹⁰) Foshay has recently obtained a serum, by prolonged immunization of goats, which is promising In a single case where I used it there was a prompt and permanent disappearance of the fever

The literature contains several favorable reports following the use of typhoid vaccine intravenously There are also some reports indicating favorable results following the use of arsphenamine

With no specific treatment of proved value, general care of the patient is probably the most rational form of therapy Bed rest, fresh air, nourishing food, with indicated symptomatic treatment, are important

SUMMARY

The incidence of this disease is probably much higher than reported cases would indicate In blood submitted for the Wassermann test about 5 per cent of specimens show agglutination in moderate titre to *Brucella* In many active cases it is impossible to get a positive agglutination test unless the test is repeated at frequent intervals In long-continued cases the clinical signs and symptoms may be relied upon to make the diagnosis

The best preventive measure is pasteurization of milk

Among farmers the porcine type of infection is often found

There is no proved satisfactory method of treatment

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GONOCOCCAL ARTHRITIS. A CLINICAL STUDY OF 69 CASES *

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ONE of the commonest causes of acute and chronic arthritis is gonococcal infection. In many patients the diagnosis is a task of no small difficulty inasmuch as the arthritis may appear some weeks, months or years after the primary infection and, indeed, it may manifest itself for the first time after the original site of infection has healed entirely. In view of the frequent difficulty in diagnosis, we have analyzed the clinical features and course of the disease in 69 cases of gonococcal arthritis which we have observed during the past three years, in an attempt to emphasize a number of features which were helpful in establishing a diagnosis. In addition, we present data regarding prognosis in this disease.

Before proceeding with the detailed analyses of the cases, it is well to recall the pathologic features of the joint lesions in gonococcal arthritis. Elsewhere, Keefer, Parker and Myers ¹ have described the histological picture of the synovial membrane in gonococcal arthritis. An appreciation of the changes is helpful in understanding the variations in the clinical picture and course of the disease so far as the joints are concerned. When there is pain, periarticular swelling and exudation of non-infected synovial fluid into the joint cavity, the pathologic process is confined for the most part to the synovial connective tissue where there are collections of polymorphonuclear leukocytes, lymphocytes and plasma cells about the blood vessels and between the strands of connective tissue. The cells upon the surface of the synovial membrane are intact and show no destruction. In these cases, it may be extremely difficult and, indeed, impossible to cultivate gonococci from the synovial fluid. In other cases in which the synovial fluid contains numerous cells and organisms, there is an extensive inflammatory reaction of the synovial membrane and underlying connective tissue. When such is the case the superficial cells of the synovial membrane are destroyed entirely, leaving only a layer of granulation tissue with newly formed blood vessels, many polymorphonuclear leukocytes and numerous gonococci. The deeper layers of the synovial membrane may not be involved extensively but there may be destruction of the cartilage and underlying bone with a resulting fibrous or bony ankylosis. The destruction of cartilage and bone may occur within a short period of time following the onset of infection, and this feature frequently aids in the discrimination of gonococcal arthritis from other types of

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chronic joint disease. Figure 1 illustrates the bone destruction that may occur in the metacarpal bone within a period of three weeks.

The diagnosis of gonococcal arthritis was made from the following points: (1) A history of a recent or previous gonococcal infection of the genito-urinary tract. (2) The presence of a localized gonococcal infection as proved by symptoms, signs and bacteriologic examination. (3) The presence of gonococci in the synovial fluid or a positive gonococcal complement fixation test in the blood serum or synovial fluid. In the event of not being able to demonstrate gonococci in the synovial fluid, care was

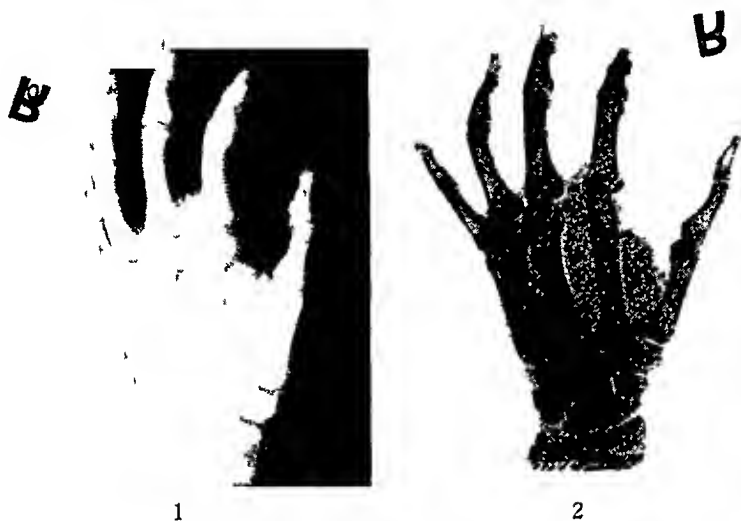


FIG. 1. (1) X-ray examination of right hand showing a normal joint space of metacarpal-phalangeal joint of the index finger. (2) X-ray of the same hand taken three weeks later showing destruction of bone, loss of joint space of the metacarpal-phalangeal joint of the index finger.

taken to exclude other types of arthritis such as rheumatic fever and tuberculous arthritis. In no case, however, was the diagnosis of gonococcal arthritis accepted without at least finding a localized gonococcal infection or a positive gonococcal complement fixation test on the blood sera or synovial fluid.

ANALYSIS OF CASES

Age The age of the 69 patients varied from 18 to 70 years. Thirty-two of them were between 20 and 40 years.

Sex There were 58 males, 11 females.

Color Sixty-four were white, four were negroes and one was an Indian.

Previous Attacks of Arthritis Twenty-one patients had had a previous attack of arthritis, and of these, 14 were definitely gonococcal arthritis. Of the remaining seven, three were due to acute rheumatic fever, and in

the other four the etiology was uncertain, it was stated that no urethritis existed at the time of the previous attack

Previous Attacks of Gonorrhea Thirty-four patients had had more than one attack of gonorrhea, and in seven additional cases the presence of a previous infection was probable. Fourteen of these patients had had gonococcal arthritis with their former attack of gonorrhea. This is a fairly high proportion in such a small number of cases, but it bears out the previously observed fact that recurrent attacks of arthritis are common with reinfection due to the gonococcus.

Time of Onset of Arthritis in Relation to the Gonorrhea The evidence obtained as to the relation of the onset of arthritis to the stage of the initial lesion was not satisfactory in every case. This was due to the presence of a chronic genito-urinary tract infection of indeterminate duration or to inaccurate observations of the patients. In one, the arthritis began simultaneously with the appearance of an attack of urethritis, in eight, it appeared between 10 and 14 days after the onset of gonorrhea, in two, within three weeks, and in three, from two to six months. In the other cases the infection was either of indeterminate duration or there had been multiple attacks of gonorrhea so that the time relations could not be determined with accuracy. In three instances all traces of the local gonococcal infection had disappeared.

The observations indicate that arthritis may appear at any time after the onset of gonorrhea, commonly after reinfection, or rarely when the local genital tract lesion has disappeared.

Relation of Onset of Arthritis and Other Complications of Gonorrhea There were 16 patients with bilateral catarrhal conjunctivitis (23.1 per cent) and three with unilateral iridocyclitis. Inasmuch as we did not see the patients until after the arthritis appeared and as, in some cases, the conjunctivitis gives rise to very few symptoms, the precise time relations between the onset of the arthritis and the ocular complications were difficult to determine. In two cases, the conjunctivitis appeared at the same time as the arthritis, in six, it had been present from one to 10 days before the onset of the joint pains, and in the others it was present at the time of the first examination and its duration could not be ascertained accurately. The conjunctivitis commonly disappeared within two weeks and before the joint pains. In only one case were relapses observed, and this was associated with a recurrence of an iridocyclitis. The discharge from the conjunctivae was scanty in amount and consisted of mucus containing leukocytes, but in no case were gonococci recovered from the exudate. Simple conjunctivitis always disappeared without any permanent damage to the eyes. Three patients had unilateral iridocyclitis, and conjunctivitis. This was extremely painful and produced a lesion resulting in diminution of vision.

One patient developed endocarditis, in this instance the arthritis pre-

ceded the signs of endocarditis but it was not clear how long vegetations had been present on the valves before the signs appeared

Death occurred in four patients, in one there was an endocarditis, in another an intercurrent lobar pneumonia, in a third death resulted from a progressive gonococcal infection, and in the fourth there was a streptococcal septicemia

Type and Extent of Local Gonococcal Lesion Associated with Arthritis Of the patients with arthritis, 54 had prostatitis, 43 urethritis, 10 cervicitis, five epididymitis, one seminal vesiculitis, and one each an abscess of Cowper's glands, Bartholin's glands and Skene's glands. Three of the women were pregnant at the time of the infection, and in three no signs of a localized infection could be found. In men, it was the rule to find involvement of the posterior urethra and prostate when arthritis was present. In an occasional case, the onset of the arthritis could be definitely related to the extension of the local process to the prostate, epididymis or Cowper's gland

Symptoms and Clinical Course The first symptom complained of was usually pain in one or more of the joints, either the small joints of the hand, or the larger joints such as the knees or ankles. The pain was often first noticed to be dull and aching in character, exaggerated by motion, and then followed by swelling and redness. Of the 69 patients, the onset appeared after a respiratory infection in 10, and in these this history gave rise to considerable difficulty in diagnosis. The degree of swelling varied tremendously so that in 40 of the cases we were able to aspirate from five to 165 cubic centimeters of fluid from the joint cavities, and in 13 this was done more than once. The effusion into the joints varied in its duration, in 27 cases it diminished after one aspiration so that it was not necessary to do another, whereas in 13 it had to be repeated from two to 11 times. The pain was usually diminished markedly following aspiration of the joints

Very often there was localized tenderness of the joints, especially, as in the knee, about the attachment of the quadriceps tendon to the patella and about the edge of the tibia

Muscular atrophy in the neighborhood of the affected joints was observed in all cases, and in many it was extreme and out of all proportion to that which could be accounted for on a basis of disease alone

Relaxation of ligaments and dislocation were not observed, but the deformities and restricted motion were due to contracture of the capsular tissues

Joints Involved Sixty patients had a polyarticular arthritis, and in the other nine it was monoarticular. The joints that were involved are summarized in table 1. From this table it is seen that any or all of the joints may be attacked during the course of the infection. The olecranon bursa was involved once. A very common lesion when the ankles, wrists and metatarsal-phalangeal and metacarpal-phalangeal joints were the site

TABLE I
Joints Involved in 69 Cases of Gonococcal Arthritis

| | |
|----------------------|----|
| I POLYARTHRITIS | 60 |
| II MONARTHRITIS—Knee | 9 |
| Elbow | 1 |

| Joints | | Tenosynovitis |
|-----------------------|----|---------------|
| Knees | 60 | 4 |
| Ankles | 34 | 25 |
| Wrists | 25 | 14 |
| Metacarpal-phalangeal | 18 | 6 |
| Shoulders | 17 | |
| Metatarsal-phalangeal | 16 | 6 |
| Fingers | 15 | 4 |
| Hips | 14 | |
| Elbows | 12 | |
| Lumbar spine | 11 | |
| Toes | 10 | |
| Sacro-iliac | 8 | |
| Heels | 7 | |
| Cervical spine | 4 | |
| Dorsal spine | 2 | |
| Sterno-clavicular | 2 | |
| Costo-sternal | 2 | |
| Temporo-mandibular | 1 | |
| Olecranon bursa | 1 | |

of infection was an associated tenosynovitis. This latter feature was outstanding in 33 cases and often it completely dominated the clinical picture. In one case, a localized tendon sheath abscess containing gonococci was seen.

Fever. An elevation of temperature above normal was observed in most of the patients. In some, it was of a few days' duration, in others, it was indeterminate and prolonged, varying from 99° to 100° or 101° F, and in a few cases reading as high as 102° to 103° F. In none of the cases was the temperature curve influenced by salicylates and there was nothing characteristic of the febrile reaction in the group as a whole.

Blood. The white blood cell count was increased in all cases, varying between 9,000 and 23,000 per cubic millimeter. The polymorphonuclear cells were increased and varied between 70 and 88 per cent. In the prolonged cases, an anemia frequently developed.

Sedimentation Reaction. The sedimentation rate was increased in all the cases, varying from 0.4 to 1.7 mm per minute according to the method of Ernstene and O'Rourke. This examination was of no specific diagnostic value as we² pointed out previously. It was, however, helpful in following the course of the active infection.

The course of the disease was so variable that diagnostic difficulties often arose. In the acute cases, the differentiation from acute rheumatic fever was sometimes difficult, and in the subacute cases, the discrimination from rheumatoid arthritis was necessary.

The differentiation from acute rheumatic fever was especially difficult in the cases presenting a history of the onset of the arthritis following a

respiratory or tonsillar infection. In these, the onset of the joint pains was often acute, and it was only by observing the lack of responses to salicylates and the absence of changes in the cardiovascular system by physical or electrocardiographic examination, and by finding positive evidence of gonococcal infection that one could be reasonably certain of the diagnosis. In the subacute or chronic cases, the diagnosis was made only after the evidence for gonococcal arthritis had been obtained by repeated bacteriologic and serologic examinations.

The presence of bilateral conjunctivitis, perichondritis, iritis or tenosynovitis associated with arthritis that is progressive and deforming was suggestive of a gonococcal etiology and often helpful in diagnosis.

Prognosis The prognosis in a given case of gonococcal arthritis is always difficult as far as the outcome is concerned. This is due, in part, to the extreme variation in the course of the disease and to a lack of information regarding the mechanism of recovery from gonococcal infection. Another factor of significance is the question of reinfection before the joint lesions have subsided completely. This was observed frequently and was followed in a large number of instances by an exacerbation of joint pains. In a previous paper,³ we called attention to the fact that in patients who showed organisms in the synovial fluid and a cell count above 40,000 the outlook was poor compared with those with a non-infected fluid and a lower cell count. Even in such cases, the outlook is not very good as far as complete recovery is concerned, since only 37 per cent of our cases recovered completely without any signs of joint disease.

It can not be denied, then, that gonococcal arthritis is a serious disease. Factors that will influence the outcome are (1) Severity of infection and reaction in the synovial cavities (2) Persistence of local infection (3) Reinfection.

Gonococcal Complement Fixation Tests These were done on the blood serum of 52 patients and on the synovial fluid in 27. Of these cases in which the blood was examined, 45 specimens were positive (80 per cent), two were doubtful and five were negative. Of the cases in which the synovial fluid was tested, 20 or 74 per cent were positive. The principal diagnostic value of the test was in the cases in which organisms could not be recovered from the synovial fluid, or in the cases in which it was not possible to find organisms in the local process. This was the case in 11 instances.

Synovial Fluid Information of considerable diagnostic value was obtained from examination of the synovial fluid, which was performed in 40 cases. For purposes of discussion they are divided into two groups, according as to whether the synovial fluid contained organisms or not. In the group of infected fluids, the total cell counts varied from 7,350 to 158,000 per cubic millimeter and for non-infected fluids from 1,800 to 78,250 per cubic millimeter. While the polymorphonuclear leukocytes predominated in both groups, they were usually higher in the infected than in

the non-infected group In the latter cases, there were more lymphocytes, monocytes and clasmatocytes In no instance, however, did they increase above 33 per cent The chemical examinations of the fluid, including total protein, sugar and non-protein nitrogen, yielded no information of specific diagnostic value The serologic examinations were detailed in the section dealing with the gonococcal complement fixation test

Comment From this analysis of 69 cases certain features require special comment They can be discussed more clearly by reporting illustrative cases We refer especially to the ocular complications, the presence of arthritis without evidence of localized genital infection, tenosynovitis, perichondritis and endocarditis

CASES WITH OCULAR COMPLICATIONS

CASE I

Case of Bilateral Metastatic Conjunctivitis, Tenosynovitis and Arthritis

A 31 year old white man was admitted to the hospital with the complaint of burning of both eyes and joint pains An acute gonococcal urethritis had been present for one month He had received anterior urethral irrigations of a 1-5000 solution of potassium permanganate Ten days before entry both eyes became inflamed There was intense burning and itching There was little exudate from the conjunctival sacs Repeated stained smears failed to disclose a gram-negative diplococcus The conjunctivitis improved following boric acid irrigations and instillation of 0.5 per cent zinc sulphate Seven days later, following a mild rigor, the left ankle became swollen, hot and tender The right knee and right sacro-iliac region also became painful

The patient had had an anterior urethritis due to the gonococcus nine years previously There were no complications at that time

On entry, the temperature was 99° F, the pulse rate was 90 per minute The patient was well developed and well nourished, and acutely ill Movement of the affected joints caused severe pain There was edema of both eyelids and photophobia The conjunctivae were only very slightly inflamed There was a small amount of pus which could be expressed from the urethra The prostate was tender, boggy in consistency and slightly increased in size There was much swelling, increased heat and tenderness of the tendon sheaths about the left ankle Movements of the ankle joint induced severe pain Flexion of the left knee caused pain Tenderness was elicited on pressure over the right sacro-iliac articulation

Stained smears of the urethral pus revealed numerous intracellular gram-negative diplococci The gonococcal complement fixation reaction on the blood was positive on three occasions The Kahn and Wassermann reactions were negative The leukocyte counts varied between 9,500 and 14,000 per cubic millimeter Roentgenologic examination of the pelvis, knees and ankles showed no bone changes

With local therapy the urethral discharge disappeared but the prostatic infection continued The lower back pain persisted About the left ankle, the increased heat and tenderness subsided gradually but slight swelling and pain on motion persisted Pain on motion of the right ankle subsided Swelling, redness and pain in the right fourth toe appeared the third week in the hospital, and later subsided somewhat The patient left the hospital three months after entry There remained slight tenderness over the right sacro-iliac articulation, slight swelling and tenderness about the left ankle and slight swelling and pain on motion of the right fourth toe

This patient illustrates, then, two common complications of gonorrhea, namely, arthritis with tenosynovitis, and bilateral metastatic catarrhal conjunctivitis. The latter complication is by no means infrequent, and occurred in 23 per cent of our cases. It is called metastatic catarrhal conjunctivitis in contrast to the purulent type which develops following the direct inoculation of the conjunctival sac with gonococci, and it must be carefully differentiated from this latter type since the prognosis in the two types is quite different.

While the metastatic conjunctivitis may be the only manifestation of a general infection, it is more often associated with other complications, such as arthritis, and for that reason its presence is of some diagnostic importance inasmuch as conjunctivitis is less common as a complication of other types of arthritis. It appears before, or simultaneously with, the arthritis. It is characterized by a bilateral injection and inflammation of the bulbar and ocular conjunctivae, with scanty mucoid discharge and slight subjective symptoms in comparison with the objective signs. The sequence of events in our cases was as follows. Following a localized gonorrhea, there appeared before, with or after the onset of arthritis a catarrhal inflammation of the ocular and bulbar conjunctivae. The upper lid was more often spared than the lower. In a few cases the lids were swollen and edema of the conjunctivae with chemosis of the bulbar portion appeared. The subjective symptoms were often minimal but burning, pricking, smarting, lacrimation and photophobia were frequent complaints. In all but three cases the process was benign, lasting about two weeks. In none of the cases were we able to recover gonococci from the exudate. The diagnosis was made on the presence of a gonorrhea, the absence of a history of infected material coming in contact with the eyes, the bilateral process, the mildness of the subjective symptoms in comparison with the objective signs, the scantiness of the exudate and the absence of gonococci.

In the three cases with iritis, the ocular manifestations were more severe. The following case illustrates the course of events in a man with iritis.

CASE II

Case with Iridocyclitis and Arthritis

A 30 year old white man entered the hospital because of painful swelling of the right knee and ankle and pain in the left knee. For two weeks, the patient had had mild lower back pain. Four days before entry, this disappeared, but there was redness, photophobia and lacrimation of the left eye. These symptoms subsided somewhat but there was blurring of the vision of the left eye. The right knee and right ankle had been acutely painful and swollen.

Gonococcal infection was denied. There had been a shrapnel wound of the right knee, with a subsequent operative procedure, five years previously. There were never any other joint lesions.

On entry the temperature was 100° F, the pulse rate was 100 per minute. The patient was well nourished and well developed. He appeared acutely ill. The conjunctiva, iris, pupil and fundus of the right eye were normal. The left pupil was con-

tracted, fixed and irregular, there was marked circumcorneal injection, the pupillary space was cloudy, the fundus could not be seen. There was no urethral discharge. The prostate was tender and boggy in consistency. The capsule of the right knee was distended. The right ankle was swollen over the dorsal and lateral surfaces. Both joints were limited as to motion because of the severe pain. There was an increase in local heat but no redness about either joint.

The increased synovial fluid in the right knee was aspirated the day following admission. Ninety cubic centimeters of yellow turbid fluid, containing 52,800 cells per cubic millimeter, were removed. Ninety-eight per cent of the cells were polymorphonuclear cells and 2 per cent were lymphocytes. Fluid reaccumulated so that aspiration had to be repeated two and, again, four days later. The cells numbered 26,450 and 9,900 per cubic millimeter, respectively. The polymorphonuclear cells made up 98 and 99 per cent of the total, respectively. No organisms were recovered from these fluids on culture. The gonococcal complement fixation reaction of the fluids, as well as the blood sera, were positive. The Wassermann reaction was negative in the specimens of fluid and blood sera.

Soon after entry there was swelling, pain and tenderness of the left wrist joint. Fluid did not recur in the right knee. The left wrist and right ankle lesions subsided gradually. One month after entry pain and tenderness over the sacro-iliac articulations appeared rather suddenly, to persist for six weeks. Following a vigorous prostatic massage six weeks after entry there was a sudden appearance of fluid in the left knee joint with an exacerbation of the iridocyclitis of the left eye. Ninety cubic centimeters of yellow cloudy fluid were removed from the left knee joint. This fluid contained 13,300 cells, of which 92 per cent were polymorphonuclear cells, 5 per cent were clasmotocytes and 3 per cent were lymphocytes. The culture of this fluid did not yield a growth of microorganisms. Ten weeks after entry the patient still complained of pain in both knees, particularly on motion. The left wrist was painful on motion and slightly swollen. There was moderate swelling but little pain about the right ankle.

Following treatment, the left eye at first improved with loss of pain and lacrimation, and the partial return of vision. The conjunctiva was not inflamed. The pupil was dilated and regular. There was a recurrence of the symptom of iritis six weeks after entry as noted. Ten weeks after entry vision remained somewhat impaired, but no other symptoms remained.

Smears of the prostatic secretion revealed numerous gram-negative intracellular diplococci. The leukocyte counts varied between 7,800 and 15,000 per cubic millimeter. Roentgenologic examinations of the articulations showed evidence of synovitis but no bony changes.

Treatment consisted of instillates of a 1 per cent solution of atropine and boric acid irrigations of the left eye, light prostatic massage, forced fluid intake, bed rest, rest of the involved joints, massage and muscle-setting exercises.

In this case, the iridocyclitis was extremely painful, interfered with vision and left its mark in that there was permanent damage to the eye. There were relapses of both the arthritis and iridocyclitis while under observation, the cause of which remains unexplained. Whether the rigorous prostatic massage was responsible for a relapse remains an open question.

The ocular complications of gonorrhea have been discussed at length by Byers⁴ in a most excellent and comprehensive monograph. He pointed out that the deep-seated congestion observed in some cases of conjunctivitis was often an expression of an inflammation of the interior structures of the eye. This is especially true when the uveal tract is involved, such

as we observed in the three cases of iridocyclitis. Byers emphasizes the fact that second and later attacks of uveitis are observed with recurrent attacks of gonorrhea. This also is true of attacks of arthritis.

CASES WITH TENOSYNOVITIS AND PERICHONDRITIS

CASE III

Case of Arthritis and Tenosynovitis without Evidence of a Localized Genito-Urinary Infection

A 21 year old man was admitted because of painful swollen joints. Five days before entry the patient sustained a slight laceration of the right thumb which required incision. Three days before admission he developed a sore throat, and swelling, pain, redness and increased local temperature of the knees and wrists. The following day, although the temperature was 104° F, the right knee and right wrist were asymptomatic. The left knee and left wrist continued swollen, red, painful and tender.

On entry the temperature was 98.6° F, and the pulse rate was 98 per minute. The patient appeared moderately ill. The pharynx was inflamed. The left knee was tender, hot and tensely swollen. There was evidently an increase in synovial fluid. The left hand and fingers were markedly swollen over the dorsal surface. Motion of the left hand and fingers or pressure caused considerable pain. There was no urethral discharge. The prostate was normal in size, shape and consistency. No prostatic fluid could be expressed.

The day following admission the synovial fluid of the left knee was aspirated. Eighty cubic centimeters of yellow cloudy fluid were removed with a cell count of 37,000 per cubic millimeter. The supra-vital preparation showed 86 per cent of polymorphonuclear cells, 12 per cent clasmatocytes and 1 per cent each of lymphocytes and monocytes. Two days later, the synovial fluid had reaccumulated and 80 cubic centimeters were removed. The cell count on this occasion was 14,300 per cubic millimeter, of which 94 per cent were polymorphonuclear cells, 3 per cent were clasmatocytes, 2 per cent were monocytes and 1 per cent was lymphocytes. The cultures of specimens of both these fluids yielded gram-negative diplococci which were identified as gonococci.

The gonococcal complement fixation reaction on the blood serum and synovial fluid during the first two weeks was negative. After the second week the gonococcal complement fixation reaction on the blood serum was consistently positive. The Kahn and Wassermann reactions were negative.

The swelling of the left knee did not recur following the second aspiration. However, the swelling of the dorsum of the left wrist and fingers persisted for two weeks before subsiding. Several superficial veins of the left forearm became thrombosed.

Treatment consisted of sedatives, bed rest, and splinting and local application of heat to the left wrist. The patient remained in the hospital for seven weeks. At the time of discharge there was limitation of complete flexion of the left wrist. There was no limitation of motion nor abnormalities of the left knee.

The outstanding features of this patient's illness were the absence of a history of gonorrhea, no clinical evidence of a urethritis, but a definite arthritis and tenosynovitis due to gonococcal infection. These observations emphasize the importance of a careful bacteriologic study of synovial fluid even in the absence of a history of gonorrhea or of the demonstration of a localized gonorrheal infection.

CASE IV

Case with Tenosynovitis and Perichondritis of Cricoid Cartilage Associated with Arthritis

A woman, 20 years of age, was admitted to the hospital complaining of pains in the joints of five days' duration. Two weeks before entry an abscess of the left Bartholin's gland appeared and three days later ruptured spontaneously. Four days before entry the right wrist became painful on motion and a swelling which was finally hot, red and very tender appeared on the dorsal surface of the wrist. The following day the left shoulder was sufficiently painful to prohibit motion of this arm. Two days before admission there was pain on swallowing and tenderness over the larynx. The left knee became painful the day of entry.

Four years previously the patient had been treated for gonorrhea for two months. Two years before the present illness there was an abscess of the left Bartholin's gland which ruptured spontaneously after one week. There had been no previous joint symptoms.

The patient was moderately obese and did not appear to be acutely ill. There was some injection of the pharynx. Pressure over the cricoid and thyroid cartilages caused pain, but there was no demonstrable swelling or redness. The dorsal surface of the right wrist was slightly swollen, red and tender. Motion of the right wrist and fingers caused pain in the area of swelling. Motion of the left shoulder, which was slightly swollen and tender, caused pain. There was tenderness over the left popliteal space.

Stained smears from the urethra and cervix contained numerous gram-negative intracellular diplococci. The gonococcal complement fixation reaction was doubtful on two occasions during the first week, and positive at the end of the second week of her stay in the hospital. The Kahn and Wassermann reactions were negative. The leukocyte count never exceeded 10,200 per cubic millimeter.

Soon after entry the palmar aspect of the right wrist became swollen and tender. Swelling and tenderness also appeared just above and posterior to the external malleolus of the left ankle. With rest in bed the symptoms subsided after 10 days. Three weeks after entry a small localized area of redness, tenderness and swelling appeared to the radial side of the distal end of the right ulna. On aspiration a small amount of purulent material was obtained which yielded on culture a gram-negative diplococcus. This was incised and drained. The patient was symptomatically improved at the time of discharge one month after entry.

This patient, then, illustrates two metastatic lesions of gonorrhea aside from arthritis, tenosynovitis which finally localized with abscess formation and a perichondritis of the cricoid cartilage.

Tenosynovitis is a particularly common complication of gonorrhea and, while it is usually an accompaniment of all types of arthritis, it occasionally occurs independently. For these reasons, its presence is often suggestive of the diagnosis of gonococcal infection. It was present in 43 per cent of the cases. (See table 1.) The tendon sheaths most frequently involved were those about the internal and external malleoli, and those over the dorsum of the hands and feet. In four patients, there was involvement of the tendons about the knee joints. Aside from these tendons, those of the palm of the hand and the Achilles tendon may be involved. (Strandberg⁵) The clinical features are quite striking, in that the skin over the tendon sheaths is swollen, hot, tense, shiny, and any movement or pressure of the affected part is accompanied by agonizing pain and discomfort.

Rarely, as in case 4, there is suppuration and it becomes necessary to incise and drain the affected part.

Perichondritis of the cricoid cartilage was a feature in case 4, and in one other patient. This complication is observed in an occasional case and one's attention is attracted to it by the patient's complaint of both painful and difficult swallowing. Pressure over the affected cartilages produces pain and discomfort, and lateral motion is particularly apt to be painful. Occasionally there is swelling and redness. Besides the involvement of the laryngeal cartilages, the concha of the ear and the cartilages of the ribs may be the site of inflammation. Of our cases, two showed pain and tenderness over the costo-sternal junctions, and this did not progress to suppuration.

These two complications, then, tenosynovitis and perichondritis, may suggest the diagnosis of gonococcal infection, especially if they are accompanied by arthritis.

Another complication of gonorrhea is endocarditis, and when it occurs in association with arthritis the etiologic diagnosis may give rise to some confusion and difficulty. The sudden appearance of cardiac murmur due to ulceration of the valves may, however, give important aid in the diagnosis. This was so in case 5.

CASE V

Case with Gonococcal Polyarthritis, Tenosynovitis and Ulcerative Endocarditis without Obvious Portal of Entry

A negress, 28 years of age, was admitted to the hospital with the complaint of pains in the joints. Six days before entry she developed pain in the metacarpal-phalangeal articulation of the left thumb. Two days later both shoulders, the right elbow, the left wrist and the left knee were also painful, tender and warm. All joints had subsided before entry except the left wrist and the metacarpal-phalangeal articulation of the left thumb. There had been profuse recurrent sweating and general sensation of fever for four days.

The patient denied the symptoms characteristic of an acute genito-urinary infection by the gonococcus. There had been moderately severe dysmenorrhea and profuse yellow vaginal discharge for one year. The menstrual period had begun eight days before entry and profuse bleeding continued.

On admission the temperature was 102° F, the pulse rate was 26 per minute. The patient was a well developed and well nourished negress who appeared moderately ill. There were small lymph nodes palpable in the anterior cervical and inguinal regions. The tongue was coated. The tonsils and pharynx were somewhat injected. The examination of the chest and lungs revealed no abnormality. The heart was of normal size to percussion, the first sound at the apex was accentuated, no murmurs were detected. The systolic blood pressure was 115 mm. of Hg, and the diastolic level was 70 mm. of Hg. Examination of the abdomen revealed no abnormalities. The external genitalia were normal. Pelvic examination was not done because of vaginal bleeding. The dorsal aspect of the left wrist showed swelling, tenderness, increased heat and redness. The swelling followed the outline of the tendon sheaths. The base of the left thumb and the left thenar eminence was red, painful, tender and hot. Motion of the thumb caused considerable pain.

The patient remained in the hospital for 18 days before death. The temperature

showed daily variations between 98° F and 104.6° F. There was profuse sweating but no associated chills. The symptoms and signs referable to the joints and tendon sheaths varied little. On the second day after entry there was heard over the base of the heart a diastolic murmur which, as time passed by, became louder, rougher and was eventually radiated over the whole of the precordium. Three days before death the systolic blood pressure was 114 mm. of Hg, and the diastolic level was 44 mm. of Hg. The classical signs of aortic regurgitation were noted. There were no embolic phenomena. Uterine cervical smears revealed no gram-negative diplococci. The gonococcal complement fixation test on the blood serum was repeatedly positive. The blood Kahn, Wassermann and Hinton tests were also positive. Gonococci were grown from one of many cultures of venous blood. In spite of the administration of iron and ammonium citrate the hemoglobin remained under 60 per cent of normal. The leukocyte counts varied between 11,300 and 33,500 per cubic millimeter. The proportion of polymorphonuclear cells varied between 85 and 92 per cent.

The necropsy revealed an ulcerative endocarditis of the posterior cusp of the aortic valve, gonococci were demonstrated on culture of the vegetation. The fallopian tubes and ovaries were normal. The cervix was not examined.

In this patient, arthritis was the condition that caused the greatest discomfort at the onset and the ulceration of the aortic valves developed while she was under observation. There were no local signs of gonorrhea and even at autopsy no evidence of an active gonococcal infection of the genito-urinary tract was found. That this is not an uncommon state of affairs is amply shown in Thayer's⁶ cases in which the portal of entry could be demonstrated in only about one-half the fatal cases. The appearance of an ulcerative endocarditis during the course of an acute arthritis, especially if there is a tenosynovitis, should always lead one to suspect a gonococcal infection.

From these four cases, it is evident that a number of clinical features aside from arthritis, may appear during the course of the gonococcal infection. In obscure cases of arthritis they may be of considerable assistance in establishing the diagnosis if they are present.

In addition to the clinical features of the disease, the bacteriologic, cytologic and serologic examinations of the blood and synovial fluid are of the highest importance in establishing a diagnosis.

SUMMARY AND CONCLUSIONS

- 1 The clinical features of 69 cases of gonococcal arthritis are presented.

- 2 Gonococcal arthritis is much more often polyarticular than monoarticular.

- 3 The presence of an associated metastatic conjunctivitis, iritis, perichondritis, tenosynovitis and ulcerative endocarditis are often suggestive and helpful features in the diagnosis of gonococcal arthritis. Illustrative cases are presented to emphasize these points.

- 4 The cytologic, bacteriologic and serologic examinations of the synovial fluid were of the greatest value in diagnosis, and of less value in prognosis.

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A NEW TREATMENT FOR VARIOUS KINDS OF COMA *

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OUR knowledge of the chemical-physiological mechanism of death is incomplete. This mechanism is perhaps best understood in certain intoxications, in which the oxygen supply is disturbed, or in certain diseases of the brain, in which large areas of brain tissue are destroyed. We are little informed, however, as to the mechanism of death in the infectious diseases. We do not understand to what final factors death may be attributed in instances of cardiac diseases, carcinoma or tuberculosis. Quite unclear also remains at times the cause of death following various operative procedures.

Also the peculiar conditions of stupor and coma, frequently anteceding death, are as yet unexplained.

More knowledge of the chemical-physiological mechanism has been accumulated in instances of the diabetic, uremic, hepatic and pancreatic coma, and also in diseases of the suprarenals and hypophysis, although much awaits further explanation.

Thus, it is not surprising that the so-called hypochloremic coma was not known until 1927. We know now that hypochloremic coma is likely to arise, whenever dehydration and hypochloremia occur, followed by uremia and coma without any significant disturbance in kidney function. This occurs especially after a diet which is poor in NaCl, or follows a loss of body fluid in instances of diarrhea, vomiting, profuse perspiration, tapping, etc. At the same time an alkalosis is present, which explains the similarity of symptoms of alkali-intoxication and of hypochloremic coma.

Not long ago I¹ reported the case of a patient whose only clinical symptom was anuria. There was no renal pathology. After two days of relative well-being the patient went into coma and died. Autopsy revealed an extensive pancreatic necrosis but no significant kidney damage. The serum contained 400 mg per cent of urea. This case represented a non-nephritic uremia apparently due to the anuria. Ambard recently expressed the belief that such an anuric uremia is not due to urinary retention, but occurs on the basis of a secondary protein breakdown.

In another case of pancreatic tumor the outstanding clinical symptom was persistent vomiting. The urine was free from NaCl and the blood showed considerable hypochloremia and a large amount of urea. The patient improved temporarily after NaCl administration. Two weeks later he developed coma and died.² The autopsy revealed a carcinoma of the body of the pancreas which had compressed the stomach and duodenum. As hypochloremia has been produced experimentally in pancreatic damage, the

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

hypochloremia in this case may be explained not only on the basis of the persistent vomiting, but also on the basis of the pancreatic disease. In both of these cases death occurred with the symptoms of non-nephritic uremia.

May I proceed now to the results of my experience as to the treatment of such patients. An apparently healthy man suddenly took sick with severe dyspnea, which soon was followed by cyanosis, myocardial failure and enormous liver enlargement. The diagnosis at this time was adhesive pericarditis. The patient improved slightly under cardiac therapy but soon developed signs of uremia and slipped into coma. The blood contained 400 mg per cent of urea. Because of previous good results which I have obtained with liver extract in patients with edema of the liver, this patient was given an intramuscular injection of Hepatrat (3 c c) (Nordmark Werke, Hamburg). Shortly thereafter the patient recovered from the coma and inquired about his condition with free sensorium. Although the uremia disappeared entirely, the patient finally died of myocardial failure.

Similar good results were obtained with liver extract administration in another patient aged 86, suffering from myocarditis, suburemia due to prostatic hypertrophy and myocardial failure. This patient lived for a year, during which time he felt well. Good results were also obtained in a case of septicemia.

E Hammerschlag³ reported similar good results in the following cases:

- 1 Liver disease of doubtful etiology, jaundice, diabetes, increased non-protein nitrogen, coma. Cured by liver extract injection.
- 2 Gastric tetany in duodenal ulcer, hypochloremia and uremia, improvement following NaCl administration. In spite of operation, uremia continued, it later subsided as the result of injection with liver extract. The patient died later as a result of peritonitis.
- 3 Acute gastro-enteritis, coma, no uremia, no hypochloremia. Cured with injection of liver extract.
- 4 Gastro-enteritis, jaundice, stupor. Uremia with normal chloremia. Septicemia with enterococcus. Cured with liver extract injection.
- 5 Empyema of the gall-bladder, coma. Operation could not be performed. Coma cleared up after liver extract injection.

Similar good results were obtained in instances of hyperemesis gravidarum, postoperative coma, extensive burns, etc.

It may be mentioned here that Robineau recently demonstrated that after operations there is an increase in urea and non-protein nitrogen in the blood. Considering the frequent presence of protein-resorption, the diminution of the intra-abdominal pressure which normally is directed toward the liver, and the circulatory failure, it becomes apparent that the danger of the occurrence of non-nephritic uremia in these cases is considerable.

The curative effect of liver extract injections in these cases is difficult to explain. I believe that the severe symptoms are due to a secondary breakdown of protein. This has been made probable by the studies of Ambard in cases of anuria. While in the hypochloremic conditions a protein breakdown frequently has been assumed, this seems to be certain only in toxic-septic conditions. In liver and pancreatic diseases the nitrogen metabolism is most likely disturbed. In hyperemesis, eclampsia and in post-operative conditions an increased protein breakdown is assumed. With the assumption in mind that the liver extract contains some liver specific constituents, perhaps hormones, the question arises whether an improved liver function might successfully counteract the consequences of an increased breakdown of proteins.

This question, I think, is to be answered in the affirmative. The action of the liver is diuretic and detoxicating. The liver converts NH_3 into urea, which in uremia may be excreted by way of the bile. The liver certainly also plays some part in the interrelationship with other glands.

An interesting point may be mentioned especially. During the process of breakdown of proteins there also occurs a breakdown of the nucleoproteids, which are converted in the liver into the nucleotids. Nucleotids are composed of either carbohydrate, phosphoric acid, guanine, adenine, or of carbohydrate, phosphoric acid and pyrimidines. While guanine and adenine are deaminized in the liver and oxidized to uric acid, the pyrimidines presumably are broken down in the liver into hydantoin and finally into carbon dioxide, urea and pyruvic acid. The pyrimidines contain the same nucleus as depressants such as veronal, amytal and luminal, while hydantoin contains the nucleus of nirvanol.

During the process of increased breakdown of proteins, the organism becomes overflowed with these substances. Although the liver is capable of converting the ammonia of the amino acids into urea, this organ is unable to get rid of the numerous products of the broken down proteins. Whenever the pyrimidine nucleus cannot be broken down any further, "auto-narcosis" of the organism is likely to occur. The sudden dramatic improvement due to liver extract injection, as seen by Hammerschlag and myself, may well be explained by the assumption that the organism apparently is liberated from the broken down protein products, which have a narcotizing effect, as the result of the increased fermentative liver action. Ruskin considers possible such "auto-narcosis" in true nephritic uremia as well as in instances of the damaging action of the broken down nuclein in cases of nephrosis. According to Baudisch and Pfalz the pyrimidine breakdown is hastened by administration of iron. Ruskin, therefore, recommends in nephrosis the administration of iron, and stomach and liver substance in order to increase the hemoglobin content of the blood and to obtain an increased iron action. Liver administration in nephrosis, as recommended by Grossman years ago, has not proved successful, nor has liver extract injection real effect in true uremia. The rapid beneficial effect of

liver extract injection in non-nephritic uremia makes a fermentative, hormonal action all the more likely as most of the patients are not anemic (See Ruskin ⁴)

Quite recently sudden improvement following liver extract injection has been observed in post eclamptic coma. The comatose mother, as well as the asphyxiated comatose infant, were saved by this therapy. In view of the postoperative protein breakdown and the factors mentioned above, liver extract injections in postoperative patients are all the more to be recommended since this treatment also has been advocated in instances of post operative thrombosis.

In spite of all these reflections it may be considered possible that the substances in liver extract which counteract the tendency to coma are not formed in the liver but only stored in it, like the "anti-pernicious" principle which is formed in the stomach but found in liver tissue.

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METABOLIC STIMULANTS WITH PARTICULAR REFERENCE TO SODIUM DINITROPHENOL *

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INDIVIDUALS coming to the medical service of The Lankenau Hospital with cardiac, nephritic, gastrointestinal, blood and other disorders, as well as diabetes and obesity, have been studied more and more in the nutritional section of the Metabolic Clinic. It is remarkable to note how many functional disturbances clear up when patients are placed on a sensible, restricted but adequate diet with the avoidance of coffee, tea, tobacco and alcohol. The writer has been interested for several years in the relationship of body weight to the optimum functioning of patients and has tried numerous methods to cause a reduction in adiposity.

The best system of weight reduction remains that of limit of intake of food and increase in output of energy. All cases ordinarily may reduce satisfactorily on restricted caloric intake but the perplexity arises when patients have restricted their food intake to a point as low as they themselves have a desire to cooperate with the physician. It comes then to the stage in the care of these patients where the doctor in charge must often resort to drugs to obtain further weight loss. For this reason great interest is being shown in the subject of metabolic stimulants and accelerants.

THE METABOLIC COEFFICIENT

Metabolic activity is the utilization of the various nutritive elements for the maintenance of the fundamental physiological processes, the storing up of energy for later use, and the continuation of immediately vital functions. The ordinary source of materials is food, but metabolic processes continue whether or not the daily intake is adequate. If food is withheld a certain length of time, the body draws from its endogenous food supply. The nature of this supply is beyond control, fats and proteins being withdrawn in varying amounts according to their availability rather than to metabolic need.

It is of practical clinical importance to keep in mind also that there are two phases of metabolism, the anabolic or storing, or the creation of potential energy, and the catabolic or destroying, or the transformation to kinetic energy for physiological needs. The principal anabolic stimulant is insulin, which enables the body to withdraw sugar from the blood and store it in the liver and muscles, epinephrine plays an important part in the catabolic function by bringing about an immediate release of energy in the form of glycogen from the liver and muscles.

The metabolic fire, that is the vital force acting in the body, is subject to an infinite number of regulating mechanisms in the form of pro-enzymes,

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enzymes and anti-enzymes acting at various points in the process of chemical change. This system of enzyme control is responsible for the variation in metabolic coefficient, that is, in the degree of metabolic intensity which characterizes different species, different individuals within a species and the same individual at different times.

All physicians have had a considerable experience with the use of thyroid extract and are familiar with its action, more recently, this metabolic stimulant is falling into disuse, except on rare occasions where its assistance is required because of some glandular deficiency. Extracts of other endocrine glands, especially the gonads and pituitary, have been tried with more or less favorable results. The writer has been successful in moderate degree with the use of whole ovary in addition to diet, having obtained in some patients a loss of as much as 75 pounds.

As is well known, the hormones interact with each other, with the brain centers and the autonomic nervous system. They control to a large degree organic function and the body chemistry, so the increased oxidation following their use results from stimulation of several other physiological processes. It is the writer's impression that a distinction should be made between such agents and those which have the power *directly* to increase or decrease the rate of combustion. There is a definite class of chemical compounds which have this power, the best known of which are methylthionine chloride (methylene blue) and the dinitro compounds, on the one hand, and the cyanides on the other.

There is assuredly a difference between the condition of a subject whose metabolism has been stimulated by improving the quality of the blood, for instance, and one whose cellular combustion has been accelerated by the action of a chemical compound such as methylene blue. Theoretically, the variation in the metabolic coefficient caused by these chemicals may be assumed to be due to their effect on the sulfhydryl-disulfide system, which is explained by Bory¹ as follows:

The five elements, nitrogen, carbon, hydrogen, oxygen and sulfur together constitute the foundation of the living edifice. Nitrogen and carbon are passive energy-potentials^{*} and remain inert until they are destroyed by the activity of the two opposed elements, hydrogen and oxygen. The rôle of sulfur in this process is to control, through its easily reversible reducing-oxidizing property, both hydrogen and oxygen to insure that neither will exceed the proper limit of activity. Sulfur, drawn principally from the amino acid cystine, combines with hydrogen in the tissues forming -SH, the -SH, or sulfhydryl group, is readily oxidized, giving place to the disulfide group (S-S). The disulfide group is then reduced and the process repeated. The tissues producing the most hydrogen sulfide (H_2S) consume the most oxygen, and their carbon-nitrogen fund is destroyed in the combustion with the release of heat and energy.

Moreover, it is thought that in living tissues there is an enzyme or catalyzing substance which initiates, or accelerates, the hydrogenizing of

sulfur, thereby starting combustion when an increased amount of heat or energy is the immediate need of the organism. This happens naturally during physical exercise, when the body is exposed to a low external temperature and after the ingestion of food (specific dynamic action). Probably there is another substance, an anti-enzyme perhaps, which inhibits sulfur reduction and in this way slows or stops oxidation. Also, since the reversibility of the sulphydril-disulfide system is known to be extremely sensitive to the pH of the tissues, it may be that the temporary acidosis caused by a poorly ventilated room directly slows the process of reduction and oxidation of sulfur.

It is not difficult to believe that the various metabolic accelerants which do not appear to disturb organic and nervous function while increasing the basal metabolism from 25 to 30 per cent have this catalyzing effect on the sulfur reducing mechanism and set in motion the whole train of events in the production of heat and energy, of an intensity commensurate with the dosage. With overdosage, the heat is generated faster than the heat regulating center is able to dissipate, there is a progressive rise in body temperature up to 115° Fahrenheit, and death occurs from heat rigor.

In accordance with this conception, a classification might be made as follows

Metabolic stimulants—exciting or rousing the vital functions to activity

Metabolic depressants—lowering functional activity

Metabolic accelerants—increasing oxidation } without any appreciable effect on or-
Metabolic retardants—decreasing oxidation } ganic or nervous function

The hormones, therefore, whether secreted within the body or administered artificially, the vitamins, the various "blood builders," drugs causing respiratory and circulatory stimulation, and perhaps even those promoting diuresis, should all be regarded as metabolic stimulants. Morphine, on the other hand, might be classified as a metabolic depressant acting through the nerve centers. The clinical condition of acidosis, of varied origin, acts as a metabolic depressant. It is difficult to determine the status of a drug such as quinine, which is said to hinder the action of the oxidizing ferments of both the blood and tissues, since the exact rôle of these ferments is not known.

SODIUM DINITROPHENOL 2-4

The most recently discovered metabolic accelerants are the dinitro compounds

Dinitronaphthol

Dinitrocresol

Dinitrophenol

The last two of these have already been commercialized and placed at the physician's disposal. Dinitrocresol has been studied in England by Dr. E. C. Dodds and his co-workers^{2, 3} and is available for clinical use under the

trade name of "Dekrysil" Of particular interest to the clinicians of this country is dinitrophenol, the compound which has been so extensively studied by the investigators at Stanford University and is now being widely used in the treatment of obesity in the form of its sodium salt

The history of the discovery and adaptation of the drug for clinical trial is so readily available in the current literature that it is unnecessary to repeat it here Suffice it to say it has been proved that this chemical can increase metabolism to a high level without causing damage to vital organs and functions The fundamental physiological phenomenon occurring when dinitrophenol enters the body is an extensive increase of the combustion which is neither directly nor indirectly the result of a stimulation of the nervous system There is no relation to cardiac action or to increase in muscular work The action is generalized and appears not to involve any special organ or body system Extensive investigations have proved that the *usual* energy materials are burned independent of the type of diet Nitrogen excretion remains normal and the fats are completely burned without giving rise to acidosis

CLINICAL EXPERIMENTS

For the purpose of determining the efficacy of sodium dinitrophenol as an accelerant of catabolism, clinical observations have been made in the Metabolic Clinic of the Lankenau Hospital on a series of patients, 35 of which serve as the basis for the present discussion The series itself will be reported more fully at a later date The majority of these patients were women and were selected more or less at random, making certain to keep in mind the published contraindications to the use of the drug The patients studied had all previously been on reduction diets and had reduced as far as they themselves believed they could possibly go by dietary methods In addition, about 35 per cent had taken thyroid extract or ovarian substance with variable results

Each patient was given capsules containing 100 milligrams of the purified sodium dinitrophenol to be taken morning and evening after meals After taking two capsules a day for a week, making certain that no ill effects were present, the dosage was increased to three capsules a day, one after each meal From time to time basal metabolic readings, and blood, urine and other metabolic studies were made

It is explained to the patients that the principal effect of the medication will be a sensation of warmth, perspiration and a loss of body weight In the majority of cases the temperature did not rise over two full degrees Fahrenheit The patients ate pretty much as they pleased It is usually in the second week of therapy that patients complain of profuse perspiration and it is most important to warn them to avoid exposure to cold while perspiring After ingestion of the drug for three weeks the temperature tends to approach normal and perspiration is less pronounced although loss in

weight continues. The basal metabolism is elevated from 12 to 40 points in practically all cases. Weight loss averaged three to six pounds during the first 10 days on one to three capsules of 100 milligrams each daily. In those individuals showing a physiological response to the drug, weight loss continued at the rate of one to four pounds each week for as long a period as the medication was kept up. In about one-third of the cases an additional loss of three to five pounds took place after cessation of the therapy, following which a level was reached where no further reduction occurred.

TOXIC EFFECTS

Hyperpyrexia

Dermatitis medicamentosa

rash, pruritus, urticaria, hives

Jaundiced appearance due to staining of tissues and blood serum

Elevation of blood pressure

Pulmonary edema

Gastrointestinal reactions

General weakness, nervousness

Headache, dizziness

Exaggeration of psychoneurotic tendencies or of any pathological condition present

Toxic symptoms generally appear when the basal metabolic rate is raised above + 50%

Five of the 35 patients complained of minor symptoms such as urticaria, indigestion, nervousness, nausea and giddiness.

Two patients of the series developed what they interpreted as "pneumonia," one after taking two capsules a day for four days and the other after having been on the treatment from time to time for a few months. On physical examination of these cases at the time of the height of the fever, some râles were heard in the chest but no definite evidences of consolidation were diagnosed. There must have been at least moisture present but whether or not this was due to a respiratory infection per se, or was the effect of the drug as an irritant on the respiratory mucosa one cannot say.

One hypertensive subject developed a marked rise in both the systolic and diastolic pressure which to date it has been impossible to bring down to normal. On the other hand, a very obese male, weighing 380 pounds and with a notable endocrine dyscrasia, showed a great increase in sugar tolerance as his weight was reduced.

Another patient, who had developed a rather severe carbuncle just before the treatment was instituted showed the jaundiced appearance said to be due to staining of the blood serum and tissues with the drug.

Pain in the calf muscles was experienced in several cases.

One man on dinitrophenol twice a day for three weeks exhibited a slight urethral discharge which was non-specific in bacteriology; four years previously he had had a Neisserian infection.

Eight patients have had colds during the treatment.

Two stopped the medication because they disliked the sensation of warmth.

The most severe reaction was in a young woman, 24 years of age, weighing 160 pounds, with dysmenorrhea and evident glandular dysfunction. She was given one capsule a day for three days, two capsules a day for three days and then started on the regulation dose of three capsules a day after meals. Ten days after ingestion of the first capsule and after losing 3½ pounds in weight, she developed diarrhea, intestinal colic, generalized edema most prominent in the face and extremities, tingling and numbness of the extremities, and an urticarial rash extending from the forehead to the feet. The wheals were about the size of a half-dollar, elevated, red and radiat-

ing heat. The temperature was 102° Fahrenheit. The medication was discontinued, the patient was placed on a milk-toast diet, given calcium gluconate and a lotion for the itching. Within four to six days, the itching and rash had subsided and at the end of another week the patient was given one capsule a day with no ill effects, the dosage was gradually raised as in the first instance and five weeks after institution of the therapy, she had lost 10½ pounds, which she considered sufficient and discontinued the medication.

Most of the patients are losing weight consistently and like the treatment. Where there are no unfavorable reactions, they note an improvement in their general physical condition and have a desire for more activity. One of the concomitant effects of the drug is a general increase in well-being, a glow of the whole body, and a brightening of the mind. Since in these patients no other signs of toxicity have been noted, this is not likely a toxic effect.

DOSAGE

It may be possible that there are extremely susceptible individuals in whom even minute quantities of the drug may prove dangerous. The writer has not seen any such cases. Several fatalities and a number of untoward effects have been reported in the literature but in many cases either the dosage was too high or the dinitrophenol was not correctly administered.

To preserve the factor of safety, no patient should be given, at the onset of treatment, more than 100 milligrams a day for seven days. In the event that an idiosyncrasy is revealed, the development of serious consequences can be avoided by prompt withdrawal of the drug. If the patient exhibits no unfavorable symptoms on one capsule of 100 mg per day for seven days, it is safe to increase the dose to two capsules and then to three capsules daily, which is the accepted therapeutic dose.

In the ordinary case, not more than 100 milligrams should be given at any one time, yet in a few cases in the present series larger doses have been given, exercising great care, with no apparent detriment to the patient. The highest dosage ever used was 200 milligrams four times daily.

Certain patients seem to be resistant to the drug and where there is no weight loss on the regulation dose, if the daily dosage is pushed beyond four capsules of 100 milligrams each, toxic symptoms, principally headache, vertigo and nausea, will develop.

ACUTE INTOXICATION

The use of dinitrophenol is too new for many cases of acute intoxication to have been reported but now that it is being dispensed by druggists without prescription, such intoxications are likely to be met with at any time and a definite, well thought out plan of procedure will be of value to the doctor called in to treat the case. Profiting by the experience of others⁴⁻⁶ the writer would suggest the following measures as the most logical to resort to in handling an emergency of this kind.

- 1 Venesection (300 to 800 c c)
- 2 Intravenous injection of 100 to 300 grams of glucose in 1000 c c of physiological saline solution
- 3 Insulin 5 to 15 units, repeated every two to four hours covered by glucose
- 4 Orange juice, sugar cubes, fluids by mouth
- 5 Cooling baths
- 6 Oxygen therapy
- 7 Morphine in sufficient dosage to allay the restlessness and apprehension

CONCLUSIONS

From the author's experience it has been concluded that sodium dinitrophenol 2-4 is an accelerant of body metabolism capable of causing a notable reduction in weight. If used without regard to a planned diet, that is, a reduction diet of 700 to 1000 calories, weight loss will not be so striking although still taking place. One would get the impression that patients may be made to lose weight continually over as long a period of time as the drug is being taken and at a rate proportionate to the quantity ingested. Used with caution, this drug should prove to be a valuable adjunct in the treatment of those individuals who find it difficult or impossible to lose weight by the usual established method.

As might be expected dinitrophenol acts most satisfactorily in patients with the exogenous type of obesity. Individuals with pituitary or gonadal glandular deficiency often tolerate the drug badly or not at all. In two patients with mild myxedema, a heightening of thyroid activity approaching the thyreotoxic state has been noted after three weeks' medication, in this event immediate cessation of dinitrophenol therapy is imperative. This drug is not a substitute for thyroid extract.

It is exceedingly unfortunate for the laity that no law now exists to prevent the indiscriminate dispensing of powerful drugs such as the dinitro compounds. The therapeutic dose of 300 milligrams daily administered in three doses of 100 milligrams each is but one-tenth to one-third of that dispensed freely over drug counters today. We have knowledge of cases that have taken 15 to 30 times this quantity though not under the care of a private physician. One wonders how high the toll of deaths is going to mount when the beauty parlors and physical culture emporiums begin to pass it around. For the protection of the public, which is one of the principal responsibilities of the medical profession, and at the suggestion of an eminent jurist, the writer earnestly recommends that sodium dinitrophenol and allied chemical compounds be included in the list of dangerous drugs, the control of the use of which is governed by the Federal Food and Drug Law. These chemicals are not yet ready for general distribution through the medical profession of the country and it is unfortunate that druggists are insensitive to the fact.

That sodium dinitrophenol, dinitrocresol and other metabolic accelerants are of real value for the reduction of body weight in certain selected patients

who find it impossible to reduce by limitation of diet, is no doubt true. The writer, however, does not unreservedly recommend their use at this time and desires to stress that the safest and best way to lose weight is under the supervision of the doctor who will prescribe a diet adequate in all essential nutritive elements but limited in caloric value to such an extent that the patient's daily physiological needs will force him to draw on the fat reservoirs of the body. When the medical profession arouses itself to its obligation of service to those individuals requiring or wanting to reduce their body weight, and outlines a sensible regime to this end, the diet sanatoriums and quacks and charlatans will have a diminishing financial return and the general health of the community will be greatly benefited.

The author desires to express his sincere thanks for the helpful and critical cooperation and suggestions of his colleagues, Dr. Anthony Sindoni, Jr. and Miss Ethel May Hobson.

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BLOOD CHOLESTEROL AND CREATINE EXCRETION IN THE URINE AS AIDS TO DIAGNOSIS AND TREATMENT OF HYPOTHYROIDISM

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THE clinical symptoms of diminished thyroid activity in their classical form, during infancy and childhood, are too well known to bear repetition. One of the most important problems in the care and treatment of congenital or acquired hypothyroidism during childhood is early recognition. It is reasonable to assume that the longer treatment is delayed, the less opportunity there is of attaining the most desirable therapeutic result. Until recent years, physical signs, clinical symptoms, and basal metabolism determinations were the most important methods of establishing the diagnosis of hypothyroidism.

In infants and children, the characteristic physical appearance, subnormal temperature, retardation of growth, and other well known symptoms of hypothyroidism present a striking clinical picture. The classical symptoms and physical appearance are not, however, always present in early infancy and the clinically questionable cases in older children make it desirable to have additional aids in diagnosis.

Basal metabolism determinations have been of invaluable aid in assessing thyroid activity in older children and in adults. The limitation of basal metabolism determinations in children below the age of eight is, however, apparent when we consider that in most cases this can be accurately carried out only by direct calorimetry (measuring heat production directly in a closed chamber). Such an apparatus is not ordinarily available to the physician. Even in older children, the lack of cooperation due to mental retardation, excitement, or nervousness often renders the test unsatisfactory in obtaining reliable information.

For the past year we have been interested in the level of cholesterol in the blood and the excretion of creatine in the urine, as possible aids in early diagnosis and in gauging treatment with thyroid medication in the thyroid-deficient child.

BLOOD CHOLESTEROL

The work done at the Lahey Clinic with hypothyroidism and hyperthyroidism in adults indicated that the level of blood cholesterol might serve a useful purpose as a further laboratory check on the severity of hypothyroidism or hyperthyroidism, since the basal metabolic rate did not always give a true picture, and the clinical impression was difficult to define. A striking relationship between hypothyroidism, blood cholesterol, basal metabolic rate, and clinical improvement was observed. They concluded from

* Read at the Chicago meeting of the American College of Physicians, April 19, 1934

their study that cholesterol reflected better the severity of hypothyroidism and the true clinical condition than does the basal metabolic rate

We undertook an investigation for the purpose of determining the blood cholesterol relationship in thyroid-deficient children, having in mind the possibility of its use as a corroborating test in controlling thyroid dosage and maintaining metabolism at a normal level. In order to establish the average blood cholesterol for the group of hypothyroid children studied, the values of this lipid were determined in 25 children (table 1) ranging in age from two months to 11 years. In this group of patients, no derangement of cholesterol metabolism was present. The average level of blood cholesterol was 190 mg per 100 c c of blood. This determination is consistent with the values found by other workers in this field as cited in the literature on blood cholesterol in infants and in older children.

TABLE I

| Sex | Age | Cholesterol | Diagnosis |
|------|--------|-------------|--------------------------|
| 1 M | 2 mos | 200 | Normal child |
| 2 F | 2½ mos | 200 | Normal child |
| 3 F | 3 mos | 185 | Pyloric spasm |
| 4 F | 5 mos | 208 | Normal child |
| 5 M | 9 mos | 185 | Upper resp infection |
| 6 M | 11 mos | 185 | Cleft palate |
| 7 F | 13 mos | 208 | Pyelitis |
| 8 M | 13 mos | 217 | Achondroplastic dwarf |
| 9 F | 14 mos | 200 | Severe malnutrition |
| 10 F | 15 mos | 147 | Malnutrition, lues (?) |
| 11 F | 2 yrs | 139 | Tuberculosis (?) |
| 12 M | 3½ yrs | 208 | Mongolian idiot |
| 13 M | 4 yrs | 167 | Fecble-mindedness |
| 14 F | 4½ yrs | 185 | Eye affection |
| 15 F | 5 yrs | 129 | Eye affection |
| 16 F | 5 yrs | 200 | Eye affection |
| 17 F | 5 yrs | 208 | P O mastoidectomy |
| 18 M | 5 yrs | 200 | Malnutrition |
| 19 F | 6 yrs | 192 | P O herniotomy |
| 20 M | 6 yrs | 192 | Tonsillitis |
| 21 M | 8 yrs | 200 | Tbc abscess chest wall |
| 22 M | 9 yrs | 172 | Observation for headache |
| 23 M | 10 yrs | 217 | Enuresis |
| 24 F | 11 yrs | 192 | Obesity |
| 25 M | 11 yrs | 217 | Epilepsy |

Originally eight boys and four girls were studied and the blood cholesterol values in these children when not under treatment ranged from 277 to 782. The presence of hypercholesteremia was definitely established in these twelve patients, and this excess of cholesterol in the blood was definitely reduced upon the administration of thyroid extract. Likewise, a marked clinical improvement followed.

Since the first communication, we have added to our list 12 more thyroid-deficient children, making a total of 24. In all of these hypercholesteremia was present when thyroid extract was not taken. In a number of the above, basal metabolism was impossible of performance and blood cholesterol was used as the guide in regulating therapy and following the clinical course.

I shall now present three patients in whom blood cholesterol was put to clinical use.

CASE REPORTS

Case 1 G M, a boy, aged $9\frac{1}{2}$ years had been under treatment previous to the undertaking of this study. It was not quite clear that he was a cretin, but after two months without treatment he presented typical characteristics.

On April 12, 1932 (up to which time he had been receiving from 2 to 3 grains (0.13 to 0.2 gm) of thyroid a day), it was decided to stop thyroid. At this time his cholesterol was 156, the basal metabolic rate was plus 47, the pulse 94, and the weight $58\frac{3}{4}$ pounds (26.6 kg). In the two months that thyroid was withheld, his weight rose to $65\frac{1}{8}$ pounds (29.5 kg), a gain of $6\frac{3}{8}$ pounds. The cholesterol rose to 454, a change of 298 milligrams, the basal metabolic rate fell 58 points, and the pulse fell 40 points. When thyroid (2 grains daily) was started, the cholesterol fell to 172, a change of 282 milligrams, the basal metabolic rate rose 48 points, the pulse rose 42 points, and he lost $5\frac{7}{8}$ pounds. After the two months without medication, the hair had grown coarse and the abdomen large, and myxedema had appeared.

Case 2 A B, a boy aged 13, entered the hospital with a blood cholesterol of 454 and a basal metabolic rate of minus 41. The bony development of the wrist was that of a five year old child. In 15 days on approximately 1 grain (0.065 gm) of thyroid extract daily, the cholesterol fell to 200 and the basal metabolic rate rose to 0.

At this time we were interested in the possibility of influencing cretins by other means, as for example, by insulin, as suggested by Chamberlain, since insulin will diminish the hypercholesteremia in diabetes. The pancreatic hormone was used for 43 days, during which period thyroid was stopped. The cholesterol rose from 200 to 454 and the basal metabolic rate fell from 0 to minus 35. When thyroid was again instituted, the cholesterol fell to 208, a fall of 246 points, and the basal metabolic rate gradually rose 71 points. In the course of a little over two weeks, the thyroid was rapidly increased from 1 to 8 grains (0.065 to 0.5 gm) and the patient was kept on this large dose for a short period, following which improvement in his appearance and mental reaction took place.

Case 3 D B, a girl 15 months old, is the youngest cretin in our group. She had a normal birth and was breast fed for three months. At three months, when breast feeding was stopped, the mother observed weakness of the child's voice, dryness of the skin and hair, and laziness in food taking and in movements. The infant was suspected of being a cretin. Basal metabolism was impossible since no enclosed respiratory chamber was available. Her initial cholesterol reading was 416 and upon thyroid therapy, starting with $\frac{1}{2}$ grain and increasing to $1\frac{1}{2}$ grains, marked clinical improvement was noted. The blood cholesterol fell gradually to 333, 312, 227 and the last few readings have been normal, 208, 179, and 147.

In this study the total blood cholesterol only was estimated. Cholesterol appears in the blood in the free state and as cholesterol ester, the relative proportions being 20 to 50 per cent of free cholesterol and 50 to 80 per cent of cholesterol ester. Schwartz and Topper suggest that the examination of the various fractions may be of further interest. They found in children with hypothyroidism not only an increase in the total blood cholesterol, but at times a disturbance of the ratio of ester to free cholesterol, of such a nature that the relative proportion is reversed, and they showed that this ratio may become normal after intensive treatment with thyroid extract. It is, therefore, possible that the determination of the ratio of free cholesterol to the ester may give us further valuable information in the diagnosis and treatment of hypothyroidism.

CREATINE EXCRETION

The discovery of the metabolic functions of creatine in muscle metabolism has attracted considerable clinical interest to the study and treatment of disorders of the muscular system, particularly in pseudohypertrophic muscular dystrophy and in myasthenia gravis. Harris and Brand¹ have reviewed this subject well.

It seems likely that creatinuria in the human is related to defective creatine storage in muscle or to abnormally high creatine synthesis. Creatinuria occurs in all types of muscular dystrophy and in states of increased endogenous protein catabolism, as in fever and in certain cases of hyperthyroidism.

Normally creatine is not found in the urine of the male adult, but small amounts of creatine are excreted periodically in the urine of normal women. In infants and children, however, creatinuria is physiological in both sexes until about the age of puberty.

From the observations in current medical literature, it appeared that the relationship of the creatine metabolism to thyroid activity in children might be of clinical interest.

Extensive creatine and creatinine excretion studies were carried out on 34 children, including normals and children with various disease conditions. Detailed observations are reported at this time on two cases of hypothyroidism in children. Twenty-four hour urine specimens were collected on two female children with hypothyroidism, one (D. J., age 6 years) for 53 consecutive days, and another (V. K., age 11) for 36 consecutive days. The preformed creatine was determined by the Folin colorimetric method and the total creatinine by the Folin-Benedict method in duplicate. The patients were on a general hospital diet containing meat once a day and approximately a quart of milk a day. Rectal temperatures were taken three times a day.

These two children showed an absence of the physiological creatinuria of childhood when not receiving thyroid therapy or creatine by mouth. The absence of creatine from the urine was not due to a low protein intake as the diet described was not creatine free and contained an adequate amount of protein. In the case of the older subject (V. K.) the experimental period was started while she was still on thyroid extract. This patient showed a gradual decrease in urinary creatine as the amount of thyroid extract administered was reduced. She continued to excrete creatine for three days after thyroid therapy was discontinued.

The hypothyroid children studied have shown a definite change in creatine metabolism. This is characterized by a diminution or complete absence of the physiological creatinuria usually found in children up until the age of puberty. Thyroid feeding restores the hypothyroid child to the condition of creatinuria characteristic of the normal child. The creatinuria is seen to be a very delicate index of the effect of ingested thyroid inasmuch as it occurs even before any definite change is noted in the basal metabolism.

and blood cholesterol It is not possible to state how the thyroid hormone affects the creatine metabolism, but it is obvious that directly or indirectly it exerts a profound and determining influence upon the character of creatine metabolism A probable explanation of the diminished creatine excretion is that it may be due to a low endogenous metabolism incident to hypothyroidism

The comparison of the changes in creatine excretion with other criteria of the efficacy of treatment in hypothyroidism is interesting It will be noted from the charts that following thyroid therapy a change in creatine excretion takes place long before there is a significant change in the basal metabolic rate, blood cholesterol, or body weight From these observations, it seems apparent that measurement of the urinary creatine is a delicate index of the effect of thyroid administration In view of the greater ease, simplicity, and reliability of creatine analysis than of the basal metabolic rate in children, it seems that this measurement may serve as a useful clinical aid in controlling thyroid medication

SUMMARY

The value of further aids in the diagnosis and treatment of thyroid-deficient children is discussed The rôle that estimation of blood cholesterol and creatine excretion plays in the urine is indicated

Blood Cholesterol The blood cholesterol is high in children with untreated hypothyroidism, and is reduced by thyroid medication

The level of blood cholesterol may be used as a guide to the efficacy of thyroid therapy

Creatine Excretion in the Urine The metabolism of creatine appears to be definitely influenced by thyroid activity during childhood

During the period from infancy until about puberty, creatinuria is physiological Hypofunction of the thyroid causes a decrease or complete cessation of creatine excretion which can be restored to normal values after the administration of thyroid extract This is accompanied by a corresponding change in the clinical condition of the patient

The creatinuria is a very delicate index of the effect of ingested thyroid inasmuch as it occurs before any definite change is noted in the basal metabolism and blood cholesterol

From a comparison with other diagnostic criteria of hypothyroidism in children, the change in creatine metabolism appears to be an important finding which may be useful in diagnosis and in the control of therapy

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SEPTICEMIA *

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Definition While the condition septicemia is well understood clinically yet it is hard to define in a clear and concise manner, hence many definitions have been offered. It is characterized by pronounced signs and symptoms of infection due largely to the presence of pathogenic organisms and their products in the blood and is usually associated with infection of the fixed tissues. In my opinion it is best defined as *an infection of the blood* because this phase greatly predominates in the clinical manifestations.

Emphasis is placed upon *infection* of the blood with all it implies as differentiated from invasion of this tissue. That is to say, the blood may be temporarily invaded by pathogenic organisms without showing any signs of infection, for this state the term *bacteremia* may be used. For example, streptococci may be found at times in the blood by culture in chronic arthritis without any signs or symptoms of infection as far as the blood is concerned. Furthermore it would appear that the gonococcus may be transmitted to the joints without clinical evidences of its temporary presence in the blood and it may be that the tubercle bacillus and other organisms may be found in the blood by culture without evidences of infection. All of this indicates that the mere presence of pathogenic organisms in the blood per se does not necessarily produce signs and symptoms of infection or constitute septicemia.

But when the immunological resistance of the blood is broken down by unusual numbers or virulence of the organisms or by other factors permitting the organisms to multiply in the blood along with the presence of toxins, aggressins or other bacterial agents, signs and symptoms of this infection of the blood are present and along with primary or secondary infection of the fixed tissues constitute the symptom complex or syndrome designated as septicemia.

In many instances this infection of the blood results in the production of abscesses or metastatic foci in other organs and tissues and especially in infections with the pyogenic cocci. When this happens the state is sometimes designated as *pyemia* or *septicopyemia* but it would appear that these terms are superfluous and unnecessary.

Since most instances of septicemia are secondary to infection of a fixed tissue some prefer to speak of the state as sepsis but this is hardly justified since it would appear that septicemia may sometimes occur without a detectable primary focus of infection or without pronounced evidences of infection.

* Trimble lecture before the Medical and Surgical Faculty of Maryland, April 24, 1934.

at the probable portal of entry of the organism, this constitutes the so-called *cryptogenic septicemia* first described by Leube about 55 years ago

Immunological Considerations Our information on the mechanism of the natural and acquired defenses of the blood against infection is very incomplete but it would appear that whatever they may be they are inadequate, break down or fail to sufficiently develop in septicemia. Hence a very important phase of treatment consists in supporting, supplying or bolstering immunological resistance whenever possible and this sometimes requires the physician or surgeon to secure the cooperation of the expert bacteriologist and immunologist. To know what to do, when to do it and to meet the changing clinical conditions without the error of attempting to do too much requires unusual experience and common sense since all cases must be strictly individualized with hardly any two exactly alike, but more of this later

Undoubtedly the blood is able to clear itself of small numbers of organisms by phagocytosis on the part of fixed cells of the reticulo-endothelial system in the liver, spleen, bone-marrow, lymph glands, etc. Indeed this phagocytosis would appear to be a very important factor in natural defense against septicemia and also in the mechanism of recovery, but apparently it requires the presence in the body fluids of adequate amounts of such antibodies as agglutinins and opsonins. In septicemia therefore the phagocytosis of organisms in the blood by reticulo-endothelium may fail or prove inadequate, not so much because the cells are "blocked," but because they are sickened by toxins or because there is insufficient production of these humoral antibodies, especially opsonins, believed to be so important in phagocytosis. These may be supplied to some extent by the timely administration of some of the immune sera in proper dosage or by the transfusion of blood from a normal or immunized donor

Furthermore the blood naturally contains variable amounts of complement which appears to bear an important relationship to natural and acquired resistance against septicemia. Unfortunately its nature, the mechanism of its action and a knowledge of ways and means for causing its increase are but imperfectly understood. In septicemia it is usually decreased and this is an additional important reason for the transfusion of blood in treatment as a means of replenishment and increasing resistance

In addition the blood naturally contains small and variable amounts of bactericidal antibody for most pathogenic organisms which may or may not produce lysis and may or may not require the presence of complement for bactericidal activity. For the want of a better term this substance is frequently spoken of as "protective antibody" and has been particularly identified with pneumococcus immunity and anti-pneumococcus serum. Unfortunately its source and the mechanism of its activity are likewise imperfectly known but it would appear to be a product of leukocytes and the cells of the reticulo-endothelial system. Its presence in whole blood or serum may be demonstrated in the test tube by the Cohen-Heist or other methods but better

in the living animal, in septicemia it appears to be exhausted. The transfusion of blood from a normal or immunized donor may furnish small amounts of this kind of antibody but larger amounts may be supplied in some of the antipneumococcus, antimeningococcus and antistreptococcus sera available for prophylactic and curative purposes.

Finally the blood may contain various natural antitoxins and it is a curious fact, to be referred to shortly in more detail, that septicemia rarely occurs in infection with diphtheria, tetanus and the bacilli of the anaerobic gangrene group which owe most of their pathogenicity to the soluble or exogenous toxins. It may be that the antitoxic properties of the blood afford a large measure of protection but neutralization of toxins by transfusion of blood and the administration of immune sera exerts an important influence in the treatment of several of the septicemias and especially those caused by various types of hemolytic streptococci, the pneumococci and meningococci.

It is apparent therefore that the natural or acquired immunological principles of the blood and the fixed cells of the reticulo-endothelial system play a very important part in resistance to and recovery from septicemia, and that treatment of the state with appropriate immunological and supportive measures ranks next in importance to the carrying out, when possible, of surgical extirpation or drainage of infected areas of the fixed tissues along with attempts at disinfection with chemical agents.

Pathogenesis In the great majority of cases of septicemia infection of the blood follows by way of the lymphatics or veins from local infection of the fixed tissues and in every case the first and most important phase of treatment consists of measures favoring the localization of the infection with prompt surgical extirpation or adequate drainage whenever possible. The primary focus, however, may be small and trivial with rapid infection of the blood when the infecting organism possesses unusual virulence and aggressiveness or when natural resistance is low, and surgical treatment requires the finest of judgment and skill since hasty operative measures may break down barriers and open avenues of extension of infection. And indeed septicemia may occur with practically no evidences of local infection at the portal of entry at all as, for example, in some cases of streptococcus, meningococcus, typhoid and anthrax septicemia. In my experience these septicemias, and especially those caused by the pyogenic cocci, invariably have the gravest prognosis, not only because it is impossible to institute local drainage, but because the absence of a well defined local lesion means the absence of a depot of local antibody production.

In the majority of cases, however, local infection of the fixed tissues occurs first with the production of lymphangitis and thrombo-phlebitis followed by invasion and infection of the blood with organisms or infected thrombi as immunological resistance is gradually or suddenly broken down. The resulting symptoms and secondary pathological changes in important organs are apparently due not so much to the organisms themselves in the

blood, as to the toxic substances they directly or indirectly produce, although the organisms as such, or in bits of thrombi, may produce embolic infections and abscesses in various organs and tissues of the body. It is for this reason that an eternal watch must be maintained for secondary infections in the course of all septicemias and especially those produced by streptococci, staphylococci, gonococci and colon bacilli with surgical drainage at the earliest favorable time whenever possible.

Bacteriological Considerations While theoretically all pathogenic bacteria may produce septicemia yet some are especially likely and others especially unlikely to produce this state. The pyogenic organisms belong to the first group, especially streptococci, pneumococci, staphylococci and meningococci, and the toxin producing anaerobes to the second. The order of frequency in which the various bacteria produce septicemia is, in my experience, as follows

Hemolytic streptococci, especially *Streptococcus pyogenes*
 Non-hemolytic streptococci, especially *Streptococcus viridans*
 Pneumococci, especially in lobar pneumonia and sinusitis
 Staphylococci, especially *Staphylococcus pyogenes aureus*
Bacillus typhosus
 Meningococci
 Gonococci
Bacillus anthracis
Bacillus coli
Spirillum recurrentis
Bacillus pyocyaneus

Among the rarer septicemias are those produced by

Bacillus mucosus capsulatus
Bacillus influenzae
Bacillus proteus
Bacillus fecalis alkaligenes
Micrococcus tetragenes

Personally I have never seen septicemia due to the true diphtheria bacillus, although some cases are on record, nor to the tetanus and other bacilli of the anaerobic gangrene group although this may be due in part to the infrequency with which anaerobic methods of blood culture are employed. Doubtless *Spirocheta pallida* produces septicemia in the early stages of syphilis but it has never been cultivated from the blood although intratesticular injections of this tissue in rabbits have produced infection. Of course many of the protozoa and some of the metazoa as well occur in the blood but do not produce septicemia in the accepted meaning of the term.

In a broad and general manner there is a relationship between virulence of the organism on the one hand and septicemia on the other. That is to say, organisms possessing a high degree of invasiveness are especially likely

to produce the state. There is, however, such an important relationship between virulence on one hand and immunological resistance on the other that curious paradoxes are frequently seen. For example, the *Staphylococcus pyogenes albus* is usually regarded as an organism of low virulence leading a saprophytic existence on the skin or mucous membranes and producing but small pimples and stitch abscesses, yet it can produce one of the most dangerous septicemias with which I am familiar. *Streptococcus viridans* is so low in virulence that it is almost impossible to kill a mouse or rabbit with it and yet what more mortal disease than its ulcerative endocarditis and associated septicemia? The anthrax bacillus produces little or no toxic substance at all and yet its septicemia with remarkably few symptoms ascribable to this state gives the disease its highest mortality. The diphtheria bacillus and even more the tetanus, botulinus and other anaerobes of wound infections are terrible producers of exogenous toxins and yet how rarely do they produce septicemia. We need to know more about those bacterial poisons which are not particularly toxic of themselves but yet are capable of preventing or retarding phagocytosis and are commonly designated as aggressins and endotoxins, for an adequate understanding of the problems involved. Certainly inadequate or complete failure in phagocytosis and "walling off" at the portal of entry would appear to be an important factor in the production of septicemia.

General Etiological Considerations—Septicemia occurs at all ages and in both sexes but somewhat more frequently in the young and in the elderly, likewise more commonly among women than men on account of puerperal infections. More cases are seen during the colder months of the year because of the higher incidence of infections of the respiratory tract with special reference to sinusitis, otitis media, mastoiditis and pneumonia.

Diabetes mellitus, chronic alcoholism and chronic debilitating diseases are predisposing factors and particularly cardio-renal disease, arteriosclerosis, cirrhosis of the liver, cancer, Hodgkin's disease, etc., in relation to terminal infections with septicemia among elderly individuals. The site of primary infection or portal of entry, and the severity of the local infection at this point show great variation, in part dependent on the organism, ranging all the way from a severe puerperal endometritis to an insignificant blister on a toe from an ill-fitting shoe, and indeed, in some cases, there is no discoverable focus at all.

Hemolytic streptococci are by all odds the most frequent producers of septicemia and especially *Streptococcus pyogenes*, the usual or commoner portals of entry of these organisms being as follows:

- 1 Minute abrasions of the skin particularly in infections with the streptococcus of erysipelas
- 2 Wounds and especially trivial puncture wounds or large lacerated ones resulting in lymphangitis
- 3 Paronychia, carbuncles, bed-sores and severe burns and, as a secondary infection, the pustules of small-pox

- 4 Puerperal endometritis or sepsis where the chances for phlebitis are particularly marked
- 5 Otitis media and mastoiditis and especially with lateral sinus thrombosis
- 6 Sinusitis with special reference to the ethmoid and sphenoid cells
- 7 Tonsillar infections secondary to scarlet fever, diphtheria and septic sore throat
- 8 Osteomyelitis, especially in young persons
- 9 Infected teeth and severe gingivitis
- 10 The genito-urinary tract, especially after instrumentation, and an occasional case secondary to suppurative appendicitis, peritonitis, suppurative cholangitis, etc

Streptococcus viridans septicemia is generally associated with ulcerative endocarditis with the portal of entry most frequently in the teeth, tonsils or sinuses

Staphylococcus septicemia is fortunately much rarer but the primary foci are similar to those listed above for the streptococci with special reference to furunculosis, infected wounds, mastoiditis, osteomyelitis and puerperal endometritis

Pneumococcus and *B. friedlander* septicemia are almost always secondary to infections of the respiratory tract and particularly lobar pneumonia, sinusitis, mastoiditis and bronchiectasis

Gonococcus septicemia is fortunately rare but usually severe and fulminating with foci in the genito-urinary tract, joints or endocardium

Meningococcus septicemia may occur as an acute fulminating infection through the mucosa and lymphatics of the naso-pharynx or as a late complication of meningitis

Anthrax septicemia is nearly always secondary to primary infection of the skin (malignant pustule) or to infection of the bronchi and intestines

In *typhoid fever* there is usually an initial bacteremia but a true septicemia may occur which is always of bad prognostic import if it appears late in the disease. *Bacillus coli* septicemia is not infrequent in conjunction with streptococci or staphylococci and especially as a terminal infection in cardio-renal and other chronic debilitating diseases or from primary foci in the biliary passages and peritoneum. *B. proteus* septicemia may also arise from infections of the urinary tract while *B. pyocyaneus* septicemia most frequently occurs in infants and young children producing rapidly fatal infections arising primarily from the gastrointestinal tract

Pathological Considerations Much may be stated about the gross and microscopic tissue changes in the various septicemias but with little advantage in such a general review of the subject as this aims to present

Suffice it to state that the changes produced in any case are inflammatory or suppurative in character and generally consist of those found (1) at the site of initial infection or portal of entry, (2) secondary foci or abscesses in different organs or tissues, (3) proliferative changes in the bone-marrow,

spleen and other organs of the reticulo-endothelial system representing immunological response to the infection with blood regeneration and (4) degenerative lesions and especially cloudy swelling and fatty degeneration of the kidneys, liver, heart, brain and other organs generally ascribed to the effects of bacterial toxins

As previously stated the tissue changes at the site of initial infection may be so slight as to readily escape detection. In my experience this has been particularly true of staphylococcus septicemia. I have seen such to be nothing more than a mere abrasion of the skin with almost complete healing at the time of a rapidly fatal septicemia, and as these lines are written I have an unusually severe case following a small and healed furuncle of the skin of a finger. In meningococcus septicemia the initial lesion may be nothing more than a moderately severe naso-pharyngitis without suppuration, but as a general rule the initial lesion of most septicemias, and especially of those caused by streptococci, show pronounced suppurative changes with septic phlebitis and lymphangitis as, for example, those occurring in mastoiditis, endometritis, etc.

The secondary foci are usually embolic in character and show many curious and unexplainable distributions in the different septicemias, involving in some instances the selective affinity of organisms for certain tissues. For example, the meningococcus localizes mainly in the meninges, the gonococcus in the muscle sheaths, periosteum of the long bones, peri-articular tissues and lungs, etc. But metastatic or embolic abscesses may occur almost anywhere, in particular they are apt to affect the kidneys, lungs, pleurae, brain, spleen and endocardium. Septic or embolic bronchopneumonia and pleuritis are always to be feared, and especially so in staphylococcus and streptococcus infections.

As a general rule the spleen is enlarged, if the patient lives long enough, and is either of the soft red type showing marked hyperplasia and phagocytic activity of the reticulo-endothelial macrophages with acute congestion of the pulp, or of the grey type with a great increase of the pulp cells and large numbers of oxidase-containing myeloid elements. The bone-marrow is apt to be opaque because of a great increase of myelocytes in response to the need for granulocytes and especially for neutrophils for combatting the infection and shows evidences of erythroblastic activity stimulated by the effects of blood destruction.

Sooner or later, depending upon the severity of the infection, the toxins and the pyrexia are apt to produce hyperemia with cloudy swelling and fatty changes especially in the heart, liver, kidneys, and adrenal glands, etc. Acute meningeal congestion, or so-called toxic meningismus with hyperplasia of the arteriolar endothelium may be observed, and is responsible for the mental symptoms of headache, delirium and coma which are so likely to be present. The much dreaded paralytic ileus I believe is due to involvement of the posterior lobe of the pituitary gland. It is expressed clinically by initial diarrhea with terminal abdominal distention, nausea and vomiting.

Laboratory Aids in Diagnosis This naturally brings one to a consideration of laboratory aids in the diagnosis of septicemia, especially, since this is essentially a bacteriological problem, with reference to study of the primary focus and blood cultures

Altogether too frequently the bacteriological examination of the primary or initial foci of infection by smears and cultures is overlooked and when septicemia is finally suspected clinically much valuable information is lacking. Furthermore the chances of developing septicemia may be sometimes estimated by a knowledge of the nature of the initial infection. For example septicemia following staphylococcus mastoiditis is rare as compared with streptococcus infections with or without lateral sinus thrombosis, streptococcus endometritis is far more likely to produce septicemia than staphylococcus or other infections and in lobar pneumonia pneumococci of group IV are less likely to produce septicemia than types I, II and III although probably the group IV septicemia is even more dangerous when it does occur.

Without doubt blood cultures are of primary importance provided the proper technic is employed. Indeed septicemia is sometimes first detected by them, and the absence of classical signs and symptoms by no means excludes the possibility of a blood stream infection. As the presence of bacteria in the blood may be intermittent, two or more cultures at intervals of one or two days may be required. As a general rule microorganisms develop rapidly in blood cultures in septicemia but all should be kept under observation for at least five to ten days before reporting sterile results.

Great care is required in taking the blood to guard against contamination with staphylococci (particularly *Staphylococcus albus*) and streptococci (particularly non-hemolytic types) from the skin. Indeed it is usually advisable to repeat the culture at least once before arriving at the diagnosis of a staphylococcus septicemia in order to guard against error due to contamination.

As shown by Ottenberg, there is an advantage in taking blood for culture from a vein draining an infected area whenever this is possible. Cultures of blood from the internal jugular veins of individuals with suspected lateral sinus thrombosis in mastoiditis have, for example, sometimes yielded positive results when cultures from veins at the elbow were sterile or have shown a smaller number of bacteria. In his opinion the finding of a much greater number of bacteria in the blood from one internal jugular vein than from the other confirms the diagnosis of lateral sinus thrombosis although it is impossible from the count alone to tell on which side the thrombosis is located.

As a general rule it is a good practice to culture relatively large amounts of blood like 5 to 10 c c, and I have found glucose hormone broth with a pH of about 7.4 to 7.6 quite suitable in 100 to 200 c c amounts. By plating measured amounts of blood like 5 c c with 10 c c of glucose hormone agar, an idea of the numbers of bacteria per cubic centimeter may be obtained which is of value in estimating the gravity of the infection as well as being a guide in evaluating the results of treatment.

Unfortunately we do not have available at present a practical method for detecting or measuring the amounts of bacterial toxins which are commonly believed to be present in the blood in septicemia. It is likely that skin tests employing the serum of the patient injected intracutaneously in the lower animals and especially the rabbit, may be of aid in this connection, but mice, rats, guinea pigs, and rabbits possess such a high natural immunity to staphylococci and streptococci, that I, at least, have not been able so far to work out an acceptable method by intraperitoneal and intravenous injections of serum.

In this connection I may also mention that it is sometimes of value to *estimate the bactericidal and bacteriostatic activity of the blood* to determine at the outset the patient's chances of developing septicemia. This is done after a method of Cohen consisting in placing a small amount of pus or culture in the bottom of a sterile test tube and adding 5 c c of blood. If organisms develop in this whole coagulated blood, it may indicate a breakdown of immunologic resistance and the possibility of the development of a blood stream infection. If organisms do not develop, the reverse may be true, although I have seen septicemia develop under such conditions apparently as the result of a subsequent reduction in immunologic resistance.

Total and differential leukocyte counts are of course well known and appreciated in the diagnosis of septicemia and should be made at frequent intervals as a guide to the severity and progress of infection. A leukocytosis due largely to an absolute increase of polymorphonuclears along with a relative or absolute decrease of eosinophiles has long been accepted as the typical change.

But an estimation of the metamyelocytes or immature polymorphonuclears greatly improves the value of the differential leukocyte count in diagnosis and also as a means of estimating the severity and progress of septicemia. These cells are readily detected and divided into two types, the young and the old or banded forms. In the usual differential count they have been included in the percentage of large lymphocytes, transitionals and polymorphonuclears and their significance entirely lost. By the newer method, however, it is possible to obtain valuable information even when the percentage of polymorphonuclears is about normal.

Normally the blood contains none of the young metamyelocytes and about 4 per cent of the older ones. In acute infections both are increased and designated by Schilling as a "shift to the left." This shift may occur with but a slight and insignificant increase of the polymorphonuclears. By dividing the number of polymorphonuclears by the number of metamyelocytes, my colleagues, Boerner and Gerard, have worked out the "nuclear index" as a means of reporting. For example, there are normally about 4 metamyelocytes to 60 polymorphonuclears giving an index of 15. If the metamyelocytes increase, the index becomes lower so that an index of 10 to 15 constitutes a slight shift to the left, 5 to 10 a moderate shift, and below 5 a marked shift. *I strongly advise the adoption of this shift to the left*

and nuclear index method for routine differential leukocyte counts and reports

Furthermore, as shown by Boerner it is advisable to abolish the usual custom of reporting the different leukocytes by percentages since it is possible for the polymorphonuclears and other types to be present in a normal percentage while being actually increased. It is much better to report the actual number of each variety per cu mm of blood, the normal for older children and adults being as follows

| | |
|--------------------|--------------|
| Lymphocytes | 1000 to 3000 |
| Monocytes | 100 to 600 |
| Polymorphonuclears | 3000 to 7000 |
| Eosinophiles | 50 to 400 |
| Basophiles | 0 to 50 |

This is a more accurate and useful method since it gives the "absolute" number of the different leukocytes, as one or more types may show important changes which are not revealed by the usual percentage or "relative" system. In septicemia particular interest is attached to the polymorphonuclears and eosinophiles and I recommend the adoption of this plan even though it entails the task of forgetting percentages and training the mind to interpret the results on the basis of the total numbers of the different leukocytes per cubic millimeter of blood.

Urine examinations are of course required with special reference to specific gravity as an index of fluid intake and output, and to albumin as an index of tubular changes. The presence of leukocytes and erythrocytes may be an index of focal glomerulo-nephritis which is likely to occur, especially in streptococcus infections. Finally bacteriological examination of catheterized specimens is indicated when embolic abscesses or pyelo-nephritis are suspected.

In this connection mention may also be made of the value of *blood chemical determinations*: urea nitrogen as an index of functional capacity of the kidneys, glucose in relation to diabetes mellitus which predisposes to septicemia and always entails an especially poor prognosis, and cholesterol which when high unfavorably influences resistance probably because of associated involvement of the adrenal glands.

And finally an *examination of the cerebrospinal fluid* is of course an invaluable aid when meningitis is suspected. The usual findings, however, are typical of the acute meningeal congestion or so-called "serous meningitis" of septicemia, i.e. a perfectly clear fluid under increased pressure with normal total cell count, with no increase of protein or decrease of sugar and bacteriologically sterile.

Symptomatology and Clinical Diagnosis My records cover 282 cases of septicemia seen in hospital and consultation practice during the past 20 years, yet it is difficult and almost impossible to present a brief account of the clinical manifestations. Indeed it seems to me that no two cases caused even by the same kind of organism are ever exactly alike and this is not to be wondered at when one remembers the possible variations due to the kind and

virulence of infection on the one hand with the age and immunological resistance of infected individuals on the other, not to mention the presence or absence of predisposing factors, the site and severity of initial infection, the distribution and severity of complications and what not

Suffice it to state that some septicemias are fulminating when virulence is extremely high or resistance extremely low, with death in a few days. The majority, however, are of the ordinary acute type running a course of one to several weeks, while a few are of the subacute or chronic type in which the septicemia or positive blood cultures may persist for many weeks and even several months with surprisingly few clinical manifestations until the terminal stage is reached—with death, as always happens in *Streptococcus viridans* endocarditis, or recovery, as sometimes occurs and especially in the streptococcus septicemia following abortion, childbirth or surgical infections.

One thing is certain, namely, that on the one hand, without blood stream infection, enough toxins may be absorbed from a severe primary focus to closely mimic the clinical picture of septicemia and that, on the other, septicemia may exist with so few of the classical symptoms as to make a positive blood culture a matter of surprise. In other words an actual finding of organisms in the blood by one or more cultures is the criterion in the final analysis and reliance cannot always be placed on symptoms alone in diagnosis.

Furthermore the *incubation period* may vary apparently from a few hours or days to several weeks. Here again virulence of infection and resistance are the determining factors. For example during epidemics of meningococcus meningitis with high virulence of the organism, healthy individuals have succumbed to the septicemia within a few days of the time of infection and before the onset of meningitis, while it is not unusual for streptococcus septicemia to develop one or more weeks after mastoidectomy, not to mention the weeks that may elapse between the infection of teeth or tonsils and the development of subacute streptococcus endocarditis with septicemia. No two cases are ever exactly alike and it is impossible to assign even approximate periods of primary incubation for the different septicemias.

Probably the most constant and characteristic clinical manifestation is the high continuous or intermittent "steeple chase" type of fever reaching its low point in the morning and peak late in the afternoon or evening. A few days of this sort of thing is usually sufficient to suggest the possibility of septicemia by a mere glance at the graphic record and especially when the fever is accompanied by chills or chilliness, a rapid bounding pulse, increased respirations, flushing of the skin with profuse sweats, a dry and tremulous tongue with thirst and sometimes unusual mental excitement or delirium soon to be followed by apathy and a comatose state.

Add to these some nausea with or without vomiting, constipation or often times a looseness of the bowels followed in a few days by gaseous distention of the intestines which may become extreme when the ileus is severe and always of bad prognostic import, various erythematous, vesicular or petechial exanthems, especially in streptococcus infections, muscular and

arthritic pains, especially in staphylococcus septicemia, the signs and symptoms accompanying the primary focus of infection, and the picture is usually complete

In the meantime there is present a sharp leukocytosis with a shift to the left, an increasing anemia with a sallow or icteroid discoloration of the skin, especially in staphylococcus and streptococcus infections, slight enlargement of the spleen and sometimes of the liver if jaundice has developed, scanty, high colored and albuminous urine and a blood culture usually positive after a day or so of incubation. Not infrequently some cyanosis is present with crepitant râles to be heard posteriorly at the bases of the lungs. Septic bronchopneumonia with pleuritis may develop. Likewise metastatic or embolic abscesses may occur in the kidneys and other organs, especially in staphylococcus septicemia, with abscesses in muscle sheaths about the shoulders, arms, legs and various joints, and with the production of periostitis and osteomyelitis. Eternal vigilance and daily examination of the patient are required because abscesses come on like a thief in the night with surprisingly few of the classical signs of dolor, calor and rubor, and they require early detection and adequate drainage.

Another thing is always certain, namely, that as long as blood cultures are positive there is some focus or foci of infection of the fixed tissues constantly feeding organisms and toxic substances into the blood so that surgical drainage is frequently of great importance in treatment whenever possible, not only of the primary focus but of secondary foci as well. Following recovery abscesses may continue to develop over months of time and especially abscesses of the muscles and bones in staphylococcus infections.

Treatment I am convinced that the treatment of septicemia will never be on a completely satisfactory basis until there is available a chemical agent or agents capable of bringing about the disinfection of the fixed tissues and blood when administered in nontoxic amounts by intravenous or intramuscular injection. Such an agent must be comparable in curative effects to the organic arsenicals like arsphenamine and neoarsphenamine in the treatment of syphilis and of other spirochetal infections. In other words I believe that chemotherapeutic research with the hope of evolving such compounds is urgently required, certainly there are no such compounds available at present although a few, to be mentioned shortly, are not without some beneficial effects. Furthermore serum therapy has not solved the problem of treatment and the general result has been that a great number of various drugs, sera and plans of treatment have been advocated with none to be particularly recommended. Space does not permit a detailed review of the enormous literature on this subject and I must content myself with a brief statement of those therapeutic procedures which I have found helpful, all of which are based upon the fundamental principles influencing infection and immunological resistance previously discussed.

In the first place adequate surgical drainage of the primary and secondary foci of infection of the fixed tissues is in my opinion of fundamental im-

portance and especially in the so-called surgical septicemias so frequently caused by hemolytic streptococci and staphylococci. This requires the very finest of surgical judgment and skill because hasty and too extensive operative measures may be meddlesome and open up new channels of infection on the one hand, while overlooking a focus or providing inadequate drainage may be disastrous on the other. On the whole, however, I believe that free drainage is the correct principle and that it is better to err on the side of too many exploratory incisions than too few. Furthermore the surgical dressings applied to accessible foci should be such as to promote the best possible drainage and in this connection I have learned to prefer hot moist dressings of hypertonic saline solution (10 per cent) or equal parts of 20 per cent saline and saturated boric acid solutions.

In hemolytic streptococcus infections I still believe in the early administration of antistreptococcus serum in adequate dosage. I doubt if such sera are bactericidal but they may contain helpful amounts of agglutinins and opsonins for the promotion of phagocytosis and likewise helpful amounts of antitoxin. A common mistake is to delay administration too long or to give too small doses. My advice is to administer serum very promptly by intravenous or intramuscular injection every 12 to 24 hours for at least four to six doses, the amount varying according as to whether concentrated or whole serum is employed, the dosage of the latter being about 30 c c by intramuscular and 50 to 100 c c by intravenous injection. There may be an advantage in testing several sera for their agglutinating titers for the streptococci secured in cultures and employing that which shows the highest titer, although the agglutinating power of a serum is not an exact measure of its efficacy, nor does the absence of agglutinins necessarily indicate that such a serum is without specific and nonspecific therapeutic value. In hemolytic streptococcus septicemias intramuscular injections of scarlet-fever antitoxin have also been used with alleged success. I have used it in seven cases of otitic origin with lateral sinus thrombosis, there were no unfavorable reactions and I gathered the clinical impression that the serum may have been of value in lessening the degree of toxemia since five of these patients recovered. In staphylococcus septicemia serum should also be administered if procurable while in pneumococcus infections due to types I and II, meningococcus, gonococcus and anthrax septicemias the prompt and free administration of the respective immune sera should be resorted to at the earliest possible moment.

Of course the necessary precautions should be observed especially when serum is given by intravenous injection. Adrenalin chloride 1:1000 is usually an effective antidote for immediate reactions when given subcutaneously or intramuscularly in dosage of 0.5 to 1.0 c c and should always be in readiness. Preliminary skin tests for allergic sensitiveness are always advisable and especially before intravenous injections. The intracutaneous test consisting of the injection of 0.2 c c of a 1:10 dilution of serum is usually employed and I generally inject the serum selected for treatment.

rather than normal horse serum. A conjunctival test consisting in placing a drop or two of 1:10 dilution of serum into one of the eyes is also employed but at this writing I am not able to express an opinion of its relative sensitivity and practical value. If either or both of these tests yield positive reactions an injection of serum should be given with special precautions, but I do not give a horse immune serum at all in any amount or by any route or method to asthmatics giving positive skin or eye reactions to such serum.

Furthermore I believe that blood transfusions are usually helpful, especially in the treatment of streptococcus and staphylococcus septicemias. It is sometimes stated that they may be harmful but I have never seen evidence of this in my experience. Personally I believe that they are always indicated and frequent small ones appear more helpful than occasional large ones. My practice is to give adults about 250 c c every three or four days for the purpose of replenishing complement and natural bactericidal and opsonizing principles as well as healthy leukocytes. When anemia is present, as it usually is in the later stages, they may be likewise helpful in combatting anoxemia by furnishing erythrocytes and hemoglobin. I have learned to prefer a direct method but the method chosen should be that with which the physician is most familiar as transfusion reactions should be avoided as much as possible and especially in very sick individuals.

In this connection it is always advisable to employ direct matching tests. Donors may be selected belonging to the same group as the patient but if time and facilities permit, the final selection of a donor should rest upon direct tests in order to avoid the regrettable error of using a donor of a subgroup. This is particularly true of Group A donors (corresponding to Group II of Moss and Jansky). I also strongly recommend in the interests of safety and simplicity dropping the Moss and Jansky classifications and employing only that of Landsteiner:

Landsteiner Group A, corresponding to II of Moss and II of Jansky

Landsteiner Group B, corresponding to III of Moss and III of Jansky

Landsteiner Group AB, corresponding to I of Moss and IV of Jansky

Landsteiner Group O, corresponding to IV of Moss and I of Jansky

Without doubt blood transfusion is a valuable part of the treatment of septicemia not only for the purpose of supplying fresh leukocytes for the elaboration of bactericidal substances if the patient's leukocytes are exhausted and incapable of immunologic response, but also for the purpose of supplying the patient with complement, as his own is likely to be reduced below normal levels.

In this connection the relative value of plain and "immunotransfusions" is commanding considerable attention but despite the fact that I have used both for many years I am as yet unable to express an opinion of value on their relative merits. The latter term was used first by Sir Almroth Wright for a method consisting of adding a quantity of vaccine, like 1,000,000,000 stock staphylococcus vaccine to about 500 c c of defibrinated blood

from a compatible donor, after waiting for about an hour the mixture was given the patient intravenously. According to Wright this procedure results in an elaboration of nonspecific bactericidal substances from the leukocytes of the donor's blood effective upon all ordinary pathogenic bacteria and not only upon the organism with which the blood had been vaccinated.

In my experience it was found that this method of "vaccinating blood in vitro" results in an increase of bactericidal activity but intravenous injections were usually followed by rather sharp reactions which I thought were caused by the bacterial protein. The therapeutic effects were due in my opinion at least in part to this nonspecific bacterial protein reaction.

Later, Colebrook and Storer suggested a method for determining whether an individual patient ought to be treated by immunotransfusion by testing the phagocytic activities of the leukocytes. If the phagocytic intake is one-third or less than that obtained with a normal blood, immunotransfusion is to be employed by the following method.

A compatible donor is given a subcutaneous injection of 1000 million stock staphylococcus vaccine and his blood used four or five hours later. Colebrook and Storer advised the use of defibrinated and not citrated blood. I have employed the method with apparent success by using direct methods of transfusion. I observed less reaction in patients and there was no danger of bacterial contamination of the blood.

Still later Hooker, Dick and others employed donors previously immunized with a vaccine prepared with the infecting organism of the individual patient. Their technic consisted in general terms of the subcutaneous injection of 500 million, 1000 million and 2000 million heat-killed bacteria on successive days followed by transfusion about one week later.

One drawback to this method is the time required for the immunization of the donor although I have found the method particularly applicable to the treatment of those cases of staphylococcus and streptococcus septicemia surviving the acute stage and requiring transfusions later on. In all instances of these septicemias it is my practice, therefore, to secure one or two compatible donors as soon as possible and start their vaccination in order to have them in readiness in from 10 to 14 days if transfusions are required as is generally the case.

At this writing, however, I am more impressed with the probable value of a method of nonspecific immunotransfusion advocated by Brody and Stephenson consisting in giving a compatible donor 50 to 75 million *B. typhosus* vaccine by intravenous injection. This usually produces a reaction of chills, fever and leukocytosis in about an hour and the blood is used three to seven hours later after the acute reaction has subsided. One drawback to the method is the unpleasant reaction in the donor requiring him to go to bed and it is therefore objectionable to professional donors. I have seen results, however, which gave me the impression that the method may be superior to plain transfusions.

Finally, since sera for streptococcus septicemia may not contain anti-

bodies for a particular strain and as antistaphylococcus serum may not be available at all, Cadham has sought to develop a method for preparing autogenous sera and administering these in conjunction with normal serum from compatible donors to furnish the complement deficiency so frequently observed in septicemia

The method adopted was as follows "The invading microorganism was obtained from blood cultures and grown in serum-glucose broth The resulting growth having been centrifuged three times in normal saline, a vaccine, in which the microorganisms had been heat-killed at the minimum lethal temperature, was then prepared and inoculated into rabbits and guinea pigs These animals tolerate comparatively large doses of a vaccine containing either streptococci or staphylococci, especially if the organisms are washed free of the media The dose of the vaccine, starting with one-quarter billion and working up to three billion organisms, was given on alternate days An agglutination titer of one to five thousand may be obtained as early as the sixth day Any time after the fifth day blood was drawn from the heart with aseptic precautions and without causing the death of the animal This blood was placed in the ice chest for eight hours, and then the serum was pipetted off The patient was inoculated subcutaneously with from 3 to 4 c c of this serum Twelve patients were treated with rabbit serum, and six with guinea pig serum There seems to have been no appreciable difference in the results obtained

"A donor whose blood was completely compatible with that of the patient was obtained as soon as possible The donor reported at the laboratory and from 50 to 60 c c of blood were withdrawn in large vacuum tubes This was left at room temperature for 15 minutes and then placed in the ice chest for 15 hours The serum was next pipetted off with all aseptic precautions, examined for sterility, diluted with equal parts of saline, and given by means of a syringe to the patient intravenously Thus, the patient received an inoculation of the animal serum containing the antibodies subcutaneously, and also received a transfusion of from 25 to 30 c c of the donor's serum containing complement Originally, the treatments were given one week apart, but this was subsequently shortened to two day intervals Treatment was continued until negative blood cultures were obtained and the patient showed considerable improvement The greatest number of treatments given to any one patient was seven

"To isolate the infective organism, culture it, inoculate the animal with the vaccine, and to await the development of amboceptors of value, required at least five days, and to obtain a serum with a more powerful agglutination titer, 12 days Frequently, the emergency of the case did not permit any such delay To overcome this difficulty some rabbits and guinea pigs were inoculated with various strains of streptococci and staphylococci Certain animals received inoculations of a vaccine prepared from 15 strains of streptococci, which had been obtained from as many different cases of local

or general sepsis. Patients were treated at once with the serum from these animals, pending the development in other animals of a specific serum."

From the standpoint of biologic therapy reference may be also made to the probable value of *bacteriophage* in the treatment of staphylococcus septicemia provided a virulent strain is available known to be highly lytic by actual laboratory test for the organism recovered from the blood. Unfortunately it is much more difficult to secure virulent bacteriophage for hemolytic streptococci and still more so for non-hemolytic strains with special reference to *Streptococcus viridans*. If bacteriophage is available I am prepared to recommend its use, especially in the treatment of staphylococcus infections. The dose may be 5 c c subcutaneously once a day or better 1 to 2 c c by intravenous injection once or twice a day. Reactions by the latter route sometimes occur but are not harmful and apparently helpful if not too severe.

Indeed I am convinced that so-called *non-specific protein reactions* are sometimes very helpful in the treatment of the septicemias, particularly if given early while the bone-marrow and other tissues of the reticulo-endothelial system have the capacity for favorable reactions. The intravenous injection of bacteriophage may have this side effect or the intravenous injection of 50 to 100 million dead typhoid bacilli may be substituted. If an autogenous vaccine has been prepared it may be used instead in doses of 25 to 50 million by intravenous injection. Otherwise one may try the intramuscular injection of 5 to 10 c c of sterilized milk but in my experience the intravenous injection of vaccine has been apparently more helpful. It is to be emphasized, however, that such agents are only to be recommended and safely used in the very early stages of septicemia and not at all in the latter stages when the patient is greatly debilitated, nor in the presence of chronic myocarditis in elderly individuals.

In this connection reference may also be made to the production of sterile abscesses by the intramuscular injection of 1 c c of turpentine diluted with 3 c c of sterile olive oil, especially in the treatment of those occasional cases of cryptogenic staphylococcus and streptococcus septicemia without discoverable primary or secondary localizations.

In addition to these measures of surgical drainage and biologic therapy recourse may be had to the intravenous injection of various chemical agents and so many have been advocated that it is at once apparent that no one of them is satisfactory. In my experience they have sometimes apparently aided in reducing the degree of septicemia but none that I know of are capable of sterilizing the fixed tissue infections which are of such fundamental importance as foci of toxin production and constant feeders of organisms into the blood. In streptococcus septicemia, particularly that of puerperal origin, I have sometimes thought that the intravenous injection of neoarsphenamine or sulpharsphenamine was helpful as suggested by Colebrook of London. The dose of either may be 0.3 to 0.45 gm dissolved in 20 to 30 c c of sterile water and slowly injected every three or four days.

Pregl's solution of iodine (concentrated) may also be tried in staphylococcus and streptococcus septicemia, the adult dose being 20 c c by intravenous injection every 24 or 48 hours. It has the advantage of low toxicity and may be safely given even in the presence of focal glomerulo-nephritis.

Rivanol in dose of 40 c c of 1/1000 solution by intravenous injection is also sometimes helpful but hardly more so than similar doses of 0.5 per cent solutions of neutral acriflavin. In my experience gentian violet in doses of 30 to 40 c c of 0.5 per cent solution by intravenous injection has not been as successful as indicated by the reports of others. However, it may be worthy of trial especially in staphylococcus septicemia but one must be sure to use the purified product prepared for intravenous injection.

The mercurial compounds must be used with caution in the presence of evidences of nephritis. I have not had the encouraging success with mercurochrome reported by many in the literature. But I still believe it may be worthy of trial in selected cases, especially in staphylococcus and *B. coli* septiciemias. The ordinary adult dose may be about 25 c c of a freshly prepared 1 per cent solution by intravenous injection or one may give 5 to 10 c c at daily intervals since a reaction does not appear necessary for therapeutic effects although in my experience best results have apparently occurred when reactions of chill, fever and leukocytosis were induced. Metaphen in dose of 20 c c of 1/1000 is much safer, produces little or no reaction and on the whole seems to be about as helpful as mercurochrome.

In addition to such biologic and chemotherapeutic treatment other measures are of great importance. Among these is to be mentioned the advisability of keeping the fluid intake to at least 3000 c c per day for adult cases and the daily intravenous injection of glucose, the average dose being 25 to 50 c c of a sterile 50 per cent buffered solution by slow injection. In some instances the continuous slow intravenous injection (*venoclysis*) of 10 per cent glucose or Ringer's solution is advisable as recommended by Hendon at the rate of no more than 200 c c per hour with interruptions in order not to exceed 3000 to 4000 c c per day. The urine should be examined at frequent intervals and the injection of glucose stopped when there is 1 per cent or more glucose present. During the height of the fever sponging with cool water is usually helpful and does much to allay mental confusion and delirium.

In the meantime the *diet* should be largely of milk, fruit juices, broths and soft foods with an attempt to furnish vitamin A and to maintain a high daily caloric intake.

It is also my custom to give one to two ounces of whiskey or brandy each day in divided doses preferably in the form of egg-nogs. Strychnine is also sometimes of service in doses of 1/30 grain two or three times a day and digitalis is occasionally required. In the presence of much pain and restlessness I do not hesitate to give pantapone and even morphine sulphate by subcutaneous injection although the latter must be used with caution if there is much distention or any nausea. Cathartics are not usually required as

daily enemas usually suffice and if there is distention these may be of 1 per cent solutions of sodium bicarbonate or about a pint of equal parts of milk and molasses at a comfortable hot temperature. Ileus is always to be feared and may be treated by such measures along with turpentine stupes for an hour and repeated every three hours along with the subcutaneous injection of 0.5 to 1.0 c.c. of surgical pituitrin every three or four hours as required. Oxygen should be given if cyanosis develops and particularly by means of a tent.

With all such measures to be considered it is easy to over-do treatment and deny the patient the greatly needed *rest* in a quiet and cool room. Indeed it is not unusual for treatment to be meddlesome in these regards and every case should have a daily therapeutic program arranged to provide the maximum of rest for the patient. It is almost impossible to foretell events and arrange treatment very far in advance, rather it must usually be arranged day by day according to individual conditions and requirements. The temperature, blood cultures and leukocyte counts are usually the best guides and blood cultures should be made every day or two whenever venapuncture is done for transfusions, the injection of glucose or chemical agents, etc.

Prophylaxis With so much to be considered in the treatment of the septicemias, especially those caused by staphylococci and streptococci, it is apparent that the methods proposed from time to time very nearly exhaust human ingenuity on this subject but yet the efficiency of a doctor in any particular case is in inverse ratio to the diversity of his armamentarium. In time, we must believe, neutralizing sera of greater efficacy will be produced, and in spite of disappointments so far, Ehrlich's "therapeuticum magnum," the intravenous drug of universal adaptation, will be discovered. But until then the need for preventive or prophylactic measures against septicemia will persist and in this connection it may be stated that a weapon of value, namely, the prophylactic use of antistreptococcus sera, is in our hands today but is not being used as frequently as should be the case.

Why should the use of antistreptococcus serum be so often delayed until severe infection is established? The immune sera are primarily prophylactics, they do not cure damaged tissues but protect those still unaffected. Furthermore their efficacy is directly related to the rapidity with which toxins are absorbed and in streptococcus infections absorption is unusually rapid. The essential is to use the serum early. If it is a good routine practice to inject antitetanic and antigangrene sera for prophylactic purposes in street accidents, although the risks of tetanus and gangrene are comparatively slight, it should be just as much a routine to administer antitoxic streptococcus serum in all cases of abnormal labor and abortion in which the incidence of puerperal sepsis is high as well as in wounds at operations on septic cases, after mastoid operations and, in fact, to any deep cut inflicted with a dirty instrument, needle pricks at postmortem examinations, etc. Little in immunology is so certain on the basis of animal experiments,

as the usefulness of such sera when given prophylactically—and their comparative uselessness when infection is well established. Neither the surgeon nor the obstetrician appears to have as yet learned these lessons. It is highly probable that the administration of such sera before or after every difficult labor and abortion would reduce the incidence and mortality of streptococcus septicemia. It is true that the patient may be made serum-sensitive but there is not the slightest reason why antisera should not be made from animals other than the horse, and in this way overcome the difficulty.

I plead therefore for the wider use of intramuscular injections of anti-streptococcus serum for prophylactic purposes and especially in puerperal and surgical cases. The dose may be 10 to 40 c c according to whether whole or concentrated sera are employed and two or three doses at three day intervals are advised.

Furthermore if septicemia is truly an infection of the blood due primarily to a complete local breakdown of barriers at the primary focus, as I believe is the case in most instances, is it not apparent that we are sometimes insufficiently drastic in surgical treatment? At first sight multiple incisions or even amputation of an arm may not seem justifiable merely for a cut finger followed by septicemia, but the price is worth paying if it is the only means of saving life. In other words a policy of undue delay in resorting to prompt and even drastic measures may result in disaster and especially in relation to prompt surgical drainage when possible and the early administration of immune sera in adequate dosage.

THE UNITED STATES PHARMACOPOEIA XI

ITS RELATION TO INTERNAL MEDICINE AND THE SCIENTIFIC NATURE OF ITS REVISION*

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SCOPE

What Should the Pharmacopoeia Contain? One of the functions of the Revision Committee is to admit into the Pharmacopoeia a carefully selected list of medicinal substances of known origin, possessing therapeutic usefulness. This object differs in no essential detail from that enjoined on the Revision Committee of the first edition published 114 years ago, which stated that the object was "to select from among substances which possess a medicinal power, those, the utility of which is most fully established and best understood." In each edition from that first one to the one now undergoing revision the principle of a carefully selected list of therapeutically useful medicines has guided each succeeding Revision Committee in fixing the boundaries of its scope.

The members of the Revision Committee derive from both the medical and pharmaceutical professions, the present Revision Committee adopted, on its organization in 1930, the policy of charging the medical members of the Committee with the final decision as to therapeutic usefulness and leaving the decision as to pharmaceutical necessity and tests for purity and strength to the pharmacist members. Carrying out this policy the entire group of medical members of the Revision Committee are members of the Sub-Committee on Scope. To these 18 physicians, practitioners, teachers, soldiers, has been given the onerous task of selecting the approximately 600 substances which enter the U S P XI.

The Scope Sub-Committee must determine what yard-stick shall measure the eligibility of a medical substance for admission. Obviously, all agents used by the profession, even if possessing medicinal properties, cannot be admitted. Therefore, the Sub-Committee on Scope has determined that a substance must be a therapeutic necessity to obtain admittance. To be considered a therapeutic necessity it must appear that its usefulness is recognized by the prevailing medical opinion, that its pharmacological activity is not completely shared by a drug or drugs already admitted, that its use is, in the aggregate, large enough to make its standardization desirable, and, finally, that its composition must not be secret, nor may it be privately controlled. Not all agents possess action making them equally important therapeutically. Laboratory study, methods of assay, animal experimentation, etc., are all of value in determining drug action, but the final arbiter

* Read at the Chicago meeting of the American College of Physicians, April 20, 1934

of therapeutic usefulness must be the clinician. Where clinical opinion is uniform or unanimous with respect to the value of a drug the work of the Scope Sub-Committee is easy, but it often happens that clinical opinion is so divided that decision as to admission is difficult. In such instances the competency of observers, the accuracy of recorded observations, as well as the number of such observations, must be digested by the Committee. It follows that many drugs favorably reported on by the pharmacologist fail to achieve a permanent place in the sun.

U S P X carried 622 titles and nearly 400 of these were admitted to U S P XI without a dissenting vote. A number of the remaining have been admitted by a two-thirds vote of the Sub-Committee on Scope. Nearly 200 new titles suggested by Committee members and others and every title in the 1931 New and Non-Official Remedies issued by the American Medical Association have been studied by the Scope Sub-Committee. The number of titles that will appear in the U S P XI cannot yet be stated, as the work of the Scope Sub-Committee has not been completed, but approximately 600 will appear. The new British Pharmacopoeia (1932) has 586 titles.

As a final check for the Sub-Committee on Scope, substances occupying a neutral zone are referred to the Sub-Committee on Therapeutics, composed of nine physicians interested in therapy. If this number appears too small a group to determine matters of such great importance, the objectors are answered by the reminder that the medical profession had adequate opportunity to have a larger influence in the work of revision. Incorporated Medical Colleges and Schools of incorporated Colleges and Universities, incorporated State Medical Associations, the American Medical Association, the U S Army, Navy and Public Health Service, are each entitled to send three delegates to the Pharmacopoeial Convention. The delegates to the Pharmacopoeial Convention select the members of the Revision Committee. Nine State Medical Associations availed themselves of the opportunity to send delegates to the 1920 Convention and 26 medical schools felt a similar interest.

Deletions. That substances admitted during one revision may be omitted in some succeeding revision is but evidence of growth in medical science and the fallibility of judgment. No criticism attaches to the first factor, in fact, growth is welcomed, the second factor does not bulk large in the work of revision because of the detailed consideration given a new substance before admission and a fixed purpose to avoid radicalism. But drugs once considered a therapeutic necessity do come to be displaced by better ones, sometimes the result of added knowledge of etiologic factors, often the consequence of better understanding of pathologic processes and equally as frequently because of new developments in drug manufacture or discovery.

Acting under these broad principles substances official in U S P X have been deleted from U S P XI. About 100 titles found in U S P X have not been admitted to U S P XI. It has not appeared wise to carry impedimenta in the Pharmacopoeia and an effort is being made to eliminate

most of the titles representing unnecessary substances. The Scope Subcommittee has endeavored to have the Pharmacopoeia represent leadership in therapy and not gravitate to the lowly estate of becoming the repository of the heirlooms garnered from the field of empiricism.

Both the medical and pharmaceutical professions are apprised of proposed deletions as the work of revision progresses and arguments in favor of retaining proposed deletions are welcomed. Either the members of the medical profession have generally approved the deletions proposed or it is peculiarly indifferent, since relatively few objections have been filed. Numerous and frequent objections have been heard from the pharmacists, individually and collectively. One would expect to find the attitude reversed, but the conclusion is inescapable that physicians are content to obtain much of their therapeutic information from the pamphlet left with the sample in their offices by a representative of a manufacturing pharmaceutical house. Too small a number of physicians feel it necessary to buy new texts on pharmacology and therapeutics and the number who purchase a copy of the United States Pharmacopoeia is almost negligible.

It has been the purpose of the Revision Committee to make the Pharmacopoeia sufficiently catholic to cover all reasonable therapeutic needs. With the substances it contains any physician should be able to carry on the exacting demands of his practice regardless of specialization. It is realized that one of the reasons the Pharmacopoeia is not more popular with physicians is because of their unwillingness to write prescriptions containing the basic agents desired, with individual directions for the pharmacist for compounding. Most physicians of this generation have either never acquired or have neglected the art of prescription writing. They prefer to write for some trade-named preparation compounded by the manufacturing house. They ignore the significant weakness of fixed ingredients, of the presence of substances the patient prescribed for may not need, of the added cost to the sick to cover proprietary rights and advertising campaigns. If the costs of medical care are too high, not a little of that cost is chargeable to physicians who prescribe high-priced drugs frequently having no greater value than older or less expensive ones.

Prescription Surveys Another yard-stick with which to measure therapeutic usefulness consists in Prescription Surveys. The object of these has been to determine the actual use of both official and non-official medicines by physicians in their prescriptions. Surveys of this nature have been made at intervals since 1885 and the latest one was made in 1931 under the auspices of the United States Pharmacopoeia and the National Formulary jointly. The object of this survey was to obtain authentic information regarding the items in prescriptions and the number of times each ingredient appeared in prescriptions written by physicians and compounded by pharmacists. The survey covered many sections of the United States, hence it was fairly representative. It also was intended to discover the extent of the use of proprietaries.

One hundred and twelve thousand prescriptions were thus studied. It was estimated that 115 million prescriptions were written during the year (1931) studied. There are two ways of expressing extent of use: (a) the number of times a given drug appeared in an arbitrary group, say 5000, (b) the total number of times a substance was estimated as being used during the year. For example, a drug may be used but once in 5000 prescriptions, this appears an infrequent use, but when it is shown that such frequency means it was used 50,000 times during the year the significance is materially altered.

Some interesting features have been uncovered by this survey. United States Pharmacopoeia titles appeared in about 70 per cent of the prescriptions studied, while non-official titles appeared in 30 per cent. About 200 of the U. S. P. X titles rarely or never appeared in the prescriptions studied. The numerical rank of appearance of drugs occurring in these 112 thousand prescriptions proved illuminating. Codeine was used three times as often as morphine, sodium bicarbonate was used more than three times as often as quinine sulphate, essence of caroid was used twice as often as dilute hydrochloric acid, sodium bromide was used five times as often as sodium iodide, the tincture of gentian compound was used more frequently than tincture of digitalis, syrup of tolu was used 13 times as often as syrup of senega, unguentum hydragry ammoniati was used six times as often as unguentum sulphuris.

Such surveys are of much statistical interest, but too much significance should not be given to mere frequency of use. Codeine sulphate was prescribed 74 times as frequently as codeine phosphate. The explanation probably lies in the familiarity with sulphate salts of alkaloids. Morphine, atropine, and strychnine being old and much used drugs, have familiarized the physician with sulphates, and when he thinks of codeine he probably only thinks in terms of a sulphate. Certainly the frequency of use of the sulphate is no sort of evidence of the superiority of the sulphate over the phosphate. Tincture of gentian compound was used oftener than tincture of digitalis, but the relative value of each is not so determined. Sodium bicarbonate was used oftener than any other drug in the Pharmacopoeia, and yet one could practice medicine without it and not raise his mortality rate. Merely because doctors used Schleich's solution, and it contained opium, did not mean that opium has any local action. The greater use of infusion of digitalis does not prove it to be a superior preparation to pulvis digitalis folium.

The Pharmacopoeia should contain a list of drugs of similar action to permit of variations for obvious reasons. But the book should be a leader of therapeutic thought, not a book of antiquity.

PATENTS AND TRADE-MARKS

The Committee on Revision was instructed by the Pharmacopoeial Convention to "admit into the Pharmacopoeia a carefully selected list of

medicinal substances of known origin, but no substances or combination of substances shall be introduced if the composition or mode of manufacture be kept secret."

The Conference of Pharmaceutical Law Enforcement Officials recommended to the Pharmacopoeial Convention that proprietary medicines be not admitted into U S P XI

A privately controlled drug is a proprietary drug. Whether it is used singly or whether more than one is used, should create no confusion in the definition. Neither does it matter if the drug is well known, possesses therapeutic value and is in general use, if privately controlled it is a proprietary. Such a drug has a name and standards of strength or purity as determined by its owner, and he may alter such standards when and as he chooses. If such a drug or product is admitted under some other name or if some other standard is set up for its preparation, it ceases to be the same drug or product, in addition, if a patent or trade-mark has been issued, the Pharmacopoeia would become liable for ignoring property rights. On the other hand, if the Pharmacopoeia should admit a proprietary product with the name and standards of the owner, it has only advertised a privately controlled preparation.

However, if a drug is marketed under a controlled name, yet other houses may produce and sell it under some other name, the Revision Committee may admit it under a distinctive title if it is thought to be a therapeutic necessity. Aspirin is an example of such a product. Any manufacturing drug house may make acetylsalicylic acid and sell it under a name not already coined. The United States Pharmacopoeia may admit such a product, select a name for it and set up standards of strength and purity. Or if a privately controlled drug loses its proprietary character it may be admitted under some distinctive name. Not a few drugs now in the Pharmacopoeia had such an origin. Fowler's solution, paregoric, Lugol's solution, Basham's mixture, are well known examples of proprietary, even "patent medicines."

After much discussion the Revision Committee adopted the following general rules with regard to drugs covered by patent or trade-mark rights:

(a) A drug covered by patent or trade-mark rights should not be considered for admission unless it possesses pharmacological activities establishing it as a therapeutic necessity.

(b) No trade-marked or patented names shall be admitted. It shall be given either a chemical name or a short coined name not patented or trade-marked.

(c) The date of expiration of patent or trade-mark shall constitute a definite factor in the decision to admit or not. If the patent expires early in the decade during which the Pharmacopoeia is official, such patent or trade-mark might not prove a serious objection to admission.

(d) The approval of the patentee or trade-mark owner should be accorded to the proposal to admit a drug so controlled.

Another interesting phase of this proprietary medicine problem was the proposal to carry under the official title of a drug all of its proprietary names.

as Synonyms To illustrate Insulin is admitted to the Pharmacopoeia under the title *insulin*, it was then proposed that such a proprietary name as Iletin be carried as a synonym The manufacturers of Iletin would thus be given a costless, yet almost priceless, advertisement It is the judgment of the Revision Committee that an iodized oil should be admitted to the Pharmacopoeia Products of this nature are marketed by a number of firms, each having a distinctive trade name of its own A few examples which may be cited are Lipiodol, Lipoiodine, Iodipin Should an iodized oil be admitted it would not be wise to carry under its U S P XI title the names just mentioned as synonyms And, unless each of these products was made exactly the same way and unless each was of the same strength as the one admitted, the other trade-marked products would not be synonyms

The following extract from the correspondence with the Rockefeller Institute relative to the admission of Tryparsamide affords an insight into some of the perplexities of trade-marks and patents and synonyms

The patent and trade-mark rights relating to Tryparsamide are held by the Rockefeller Institute and the patents in the United States expire in 1935 Merck and Company has been licensed by the Institute to manufacture Tryparsamide in the United States and in certain other countries For reasons the Institute now plans to continue to allow Merck and Company the right to sell Tryparsamide under its trade-mark rights after its patent rights have expired The Institute would have no objections whatsoever to the inclusion of Tryparsamide in the Pharmacopoeia or its proper chemical name However, we would not be prepared to abandon the name Tryparsamide or to encourage the substitution of any other title which might tend to create confusion

The Revision Committee can admit this product under its chemical name or some other coined title and set up standards for its manufacture, but if the word "Tryparsamide" is not introduced as a synonym a large part of the profession would not recognize it as Tryparsamide and they would continue to prescribe the original patented article

Favoring the plan of using synonyms, it was urged that the proprietary name was often the one best known to the physician and that he could thus better identify the official drug It was further urged that such a plan would make more effective teaching the use of official drugs to medical students The Revision Committee has decided against the proposal to admit such names as synonyms by a large majority

The whole question of patents and trade-marks in medicine is becoming one of increasing importance to the profession beyond the scope of Pharmacopoeial revision One wonders if the members of the profession are actuated by impulses involving pecuniary benefit directly or indirectly to a greater degree than obtained in the generation of physicians this one succeeded The magnanimity and fine scientific spirit which gave serums and vaccines to the world contrasts strongly with the advent of *insulin*, *ventriculin*, *viosterol* or *scarlatinal toxin*

The arguments made or rather I should say the explanations offered

in justification for seeking and obtaining patent and trade-mark rights are replete with protestations of scientific interest, of jealous concern for the welfare of the sick and solicitude for the public's purse. One of these writes, "The main object in securing patents and trade-mark rights and in licensing one company to manufacture and sell the drug has been to insure to the public a product of acceptable quality at a reasonable price."

Another representing a group controlling a product writes

The function of the Committee is to protect the public as far as possible against inadequate preparations. Thus it falls within our duties to try out new preparations, if they are successful, to approve them for distribution. If they are unsuccessful, in our opinion, it is our duty to stop their distribution. We regard the public welfare as of far greater importance than any personal relationships. We shall not hesitate to institute whatever legal proceedings are indicated.

One wonders if a patent issued on a given biological product enables a committee owning the patent to censor and control all investigation of a transmissible disease problem, one wonders if a patent is intended to interfere with independent study and experiment, one wonders who protected this same public while experimental work was being done on the product for which a patent has been issued.

Studying the broad field of research medicine, it is significant that the favorite plan now is to give some university or laboratory or committee the patent and trade-mark rights and to assure the public, as well as the profession, that all profit is to be devoted to further research. Such a plan assures the individual physician immunity from the charge that he is pecuniarily interested in the product. But it does not suppress the thought that he has made himself valuable to his institution and salary increases are not impossible.

Are we drifting away from the fine spirit of our fathers? Is the beneficent altruism of the old Masters in danger of being lost?

As a means of checking the present tendency it is suggested that the patent and trade-mark laws as pertaining to medicine be modified to the extent that when and if a product be admitted to the United States Pharmacopoeia the patent and trade-mark rights end with such admission. Were this done, coupled with interim revisions, the public, concerning which such solicitous anxiety is manifested, would be adequately protected.

FEDERAL AND STATE FOOD AND DRUG ACTS

Revision of the Federal Food and Drug Act in some form will, in all probability, be enacted into law during the present Congress. The details, merits or demerits of this proposed legislation are not proper subject matter for this discussion, but the relation of the Pharmacopoeia to such legislation, both National and State, has a real significance.

The United States Pharmacopoeia is not a governmental instrument. The Pharmacopoeias of most other countries are issued by the government,

hence are governmental institutions. The United States Pharmacopoeia is made possible through the cooperative labor of the medical and pharmaceutical professions. It did not receive any sort of recognition by the Federal government until the passage of the Food and Drug Act in 1906. At that time the necessity for having standards of purity and strength was recognized and the United States Pharmacopoeia was selected as the instrument for setting up such standards. This recognition is a most unusual one in that it is the only professional contribution which has been given such distinction. Stripped of all superfluous verbiage, it means that two professions uniting in a common effort to establish high standards in what amounts to self-regulation have done so to the extent that the Federal government has adopted those standards for purposes of enforcement of Federal laws. If an added responsibility were needed to encourage each subsequent Revision Committee to carry on, this governmental relation surely affords it. Since the major portion of the work of determining standards of purity and strength has been done by the pharmaceutical members of the Revision Committees, past and present, theirs is the larger share of credit for the present status.

The National Formulary has been included in previous Food and Drug Acts as one of the standards for determining violations of the Federal Law as to purity, etc. The present and pending bill in Congress introduces another text into the enforcement picture by defining the term "official compendium" as meaning the United States Pharmacopoeia, the Homeopathic Pharmacopoeia of the United States and the National Formulary.

Since the Homeopathic Pharmacopoeia has not been revised since 1914, it would appear that the proponents of the pending legislation have peculiarly overlooked the progress of medicine, pharmacy and chemistry, for two decades. It is admittedly difficult to set up an "Official Compendium" to be used in enforcement of a Federal Food and Drug Act without, at the same time, making such texts, in effect, the law. Congress has the power, it is thought, to recognize a work as a statutory authority in existence at the time a bill is passed, it may even include supplements to such a volume. But the pending bill would make all future editions and supplements likewise the law, and by such declaration would give future Revision Committees the authority to change standards when and if deemed desirable. Since the Revision Committees of these texts are not officers of the Government, the question might well be raised, is this an "unconstitutional delegation of legislative authority?"

The pending legislation provides, in addition, that the Secretary of Agriculture may prescribe texts or methods of assay for determining whether or not a drug complies with legal standards "when such texts or methods of assay as are prescribed are insufficient" after he has brought the fact of such insufficiency to the attention of the Revision Committees of such compendium and they have failed to provide adequate standards.

The officers of the Food and Drug Administration of the Department

of Agriculture are the enforcement officers of the Federal Food and Drug Law. This group is represented by delegates to the Pharmacopoeial Convention and has participated in work of revision since. The Bureau of Standards, likewise, is represented. By such cooperation the Pharmacopoeia is made to anticipate governmental needs through interim revisions when necessary.

The tendency of the courts to admit a wider variety of proofs of illegal manufacture or shipment of drugs outside the Pharmacopoeial standards must be noted. In the recent decision of the U. S. District Court of the Eastern District of New York, in what has come to be known as the "Ginger" case, it was held that "There is no reason to hold that the non-correspondence of the extracts shipped with the standard of the Pharmacopoeia must be shown only by chemical analysis. On the contrary, it may be established in any other logical and convincing way."

This attitude is further evidenced by the statement of an official of the Food and Drug Department that in the event the Pharmacopoeia omitted certain agents, the Government would not be likely to permit such omission seriously to handicap the department in its work of preventing impositions on the consuming public.

Another interesting angle in the relation of the Pharmacopoeia to the Federal Food and Drug Act now in force has developed in consequence of the interpretation of the Solicitor of the Food and Drug Administration of what part of the text was applicable. The Act requires compliance with the "tests for quality, purity and strength" as laid down in the Pharmacopoeia, but the Solicitor has ruled that this be interpreted as excluding such parts of the text as definitions, formulae and descriptions.

In the case of some titles in the text the definition and the description are important as to identification and even standardization. It has been quite generally accepted that the whole text of a drug was intended to be used for the establishment of uniformity, as well as efficiency.

To meet this situation it is proposed to introduce in the forthcoming Pharmacopoeia a "General Notice" definitely stating that all sections of a monograph, unless specifically exempt, are to be recognized as a part of the standard.

"INTERIM REVISION"

It is recognized by physicians, pharmacists and government officials alike that a decennial revision of the Pharmacopoeia does not keep it abreast of scientific medical development. Many new data accumulate, now, in a 10 year period, new therapeutic agents come into use at a rapid rate and refinements of manufacture, assay, etc., render old methods and standards rapidly obsolete. To appreciate the extent of this development one needs but to call to mind a few illustrations: liver extract, insulin, vitamins.

The cost of more frequent complete revisions, encompassing the issuance of an entirely new book, is prohibitive. If sectional revisions be

done the difficulty of giving them a permanent form, as well as necessary publicity, becomes a matter of practical importance. Even when the new matter involves the admission of a new agent and even if added as a "supplement," the matter of indexing offers a problem. If the change applies to but a part of the text on a given agent, the difficulty becomes appreciably more intricate.

A loose-leaf type of book, allocating one or as many sheets as necessary to each separate subject, permitting removal of the old text and insertion of the new, would seem to be the simplest method for keeping the text up to date. A nominal charge could be made for newly-revised sheets, a revised index could be made yearly and supplied each subscriber. The plan at present agreed upon to keep the U S P XI revised consists in (a) issuing a printed supplement on the first of each year, (b) the statement that each change so made becomes official on January 1, coincident with issuance, (c) that as changes are decided upon announcement be made in the medical and pharmaceutical press of the country, (d) that the supplements be of uniform size with the original text, (e) that a revised index be issued with each annual issue of supplements, (f) that a binder be supplied for the preservation of supplements as issued, (g) that a page of coupons be included in the original copy of the U S P XI, the owner of the book to fill out a coupon for each annual supplement revision, which enables him to obtain from the publisher a copy at a nominal cost, (h) the issuance at the end of five years of the original volume with all interim revisions included. This latter proposal has not been definitely determined.

The success of such a general plan of interim revision would depend upon many factors wholly beyond the control of the Revision Committee and the Board of Trustees. If the owners of the volumes did not cooperate to the extent of both obtaining and preserving the copies of interim revisions, much confusion and error would obtain. In court procedure for example, the necessity for establishing the text of the copy of the U S P XI revised to January 1 of the current year would be obvious. Another problem is presented in the books on pharmacology used by physicians and students. The text of these books is based on the United States Pharmacopoeia and the authors would meet a practical difficulty in dealing with interim revisions.

The advantages, however, are so obvious that making the plan of interim revision workable becomes a necessary duty and its accomplishment will be the outstanding achievement of Pharmacopoeial revision. Reference has been made to some of the necessities for and advantages of an up-to-date Pharmacopoeia under the section of this paper on the scope of the Pharmacopoeia.

ORIGINAL STUDY

In revising the Pharmacopoeia the medical and pharmaceutical literature is studied so that the last information available on all subjects may be

utilized. This applies to such subjects as are admitted because of therapeutic usefulness, as well as pharmaceutical necessity. Supplementing such study as the Committee on Revision has time or qualification for doing, the By-Laws of the United States Pharmacopoeia Convention authorize the employment of experts in the various fields studied. These studies began as early as 1926, preparatory to the revision of the present Pharmacopoeia.

The advantages of this plan are apparent, but three merit emphasis in the present discussion. (1) Such workers are already familiar with the current literature on the given subject, as well as the technical aspects involved. (2) By enlisting the interest of scientists, practical workers and students, as well as universities, colleges and laboratories, a greater and more general interest in the Pharmacopoeia is obtained. (3) Such coordination and intensive study means a saving in both time and money. Approximately \$10,000 have been expended on this phase of the work of revision for the coming issue.

In addition to these groups of experts the services of another valued group have been made available through the cooperation of auxiliary members. These auxiliary members were individual physicians, pharmacists and scientists who were invited by the Revision Committee to cooperate in the work of revision because of special qualifications or interests. More than 200 auxiliary members have been elected to these positions and their contributions have been noteworthy.

Yet a third group has done yeoman service in the work of revision. The United States Pharmacopoeia is the legal standard for the Philippines, Puerto Rico and Hawaii and the adopted standard of the Republic of Cuba. Representatives from these islands have, on invitation, participated in the work of revision.

Finally, the work of revision has been materially advanced by the cooperation of the Pharmacopoeial Committees of Great Britain and of Continental Europe. Switzerland, Holland and Germany have issued new Pharmacopoeias since 1926 and much of their new material has been translated by the Committee of U. S. P. XI for study by the various sub-committees.

VITAMINS

An optional method for the biological assay of one of the potent principles of cod liver oil was included in the U. S. P. X. By this act the United States Pharmacopoeia took advanced ground ahead of the Pharmacopoeia of other countries.

This method of assay was (a) optional, (b) provided that oil should contain "at least 50 units per gram," (c) provided for vitamin A assay only.

It therefore, did not establish a standard of A potency, but rather determined the lowest value an oil might have to permit labeling as a United States Pharmacopoeia product. Neither did it recognize the D

content of cod liver oil. The method of biological assay established as the end point the relief of symptoms of vitamin A starvation in young albino rats with a specified gain in weight during the test period. The cure of xerophthalmia has been urged as a superior biologic criterion, while such a criterion is more convincing qualitatively, it is more indefinite quantitatively than the criterion of growth recovery for a 35-day period.

A presumptive defect in the method of the U. S. P. X lay in the influence which other possible factors might have over the weight decline of the test animal while vitamin A was withheld, as well as such influence on the weight recovery period during the cod liver oil feeding period. One need merely mention the physical character of the ration, the amount of protein consumed and the presence of vitamins B and D.

An assay method for vitamin D had also become a necessity by virtue of increasing knowledge of its importance. The method of basing the unit for A on the daily dose, while the unit for D was based on the total dose, gave results indicative of a marked apparent discrepancy in A and D content in a given sample of oil. Some method whereby this apparent discrepancy might be reconciled was urgently needed.

Another important question in the biological assay of cod liver oil concerns the quantitative interpretation of the data of A and D assays. In all bio-assay work a certain deviation of biological response is usual. In other words, should this deviation response be ignored or made use of by specifying the unit dose in terms of percentage of positive responses? Further, some appreciation of the importance of the variations of statements on the labels of different brands of cod liver oil was made necessary because of differences in standards for potency adopted by the various distributing firms. Likewise, some uniformity in labeling was recognized as a necessity. Some firms labeled their product in terms of units per gram, others in terms of units per ounce. This lack of uniformity was confusing alike to the doctor, the druggist and the patient.

The Permanent Commission on Biological Standards of the Health Organization of the League of Nations has issued a standard for vitamins. The United States has a representative on this Commission.

Through its Board of Trustees the U. S. P. XI is cooperating with the medical and pharmaceutical professions of other countries to reach an agreement on an international standard for vitamins.

The Pharmacopoeia has set up a Vitamin Advisory Board, this includes a group of laboratories now engaged in the work of developing satisfactory vitamin assay methods for vitamins A and D. A composite sample of cod liver oil labeled "reference cod liver oil" has been distributed among the workers to be used as a standard of comparison in assaying the vitamin content of both foods and medicines. The members of the American Drug Manufacturers Association, the Federal Food and Drug Administration and a number of laboratories in various universities are cooperating with the U. S. P. XI in this work. Without this contribution on the part of

vitamin experts the expense of this work would be large enough to make it impossible for the Pharmacopoeia to carry it on

The most important question touching the work on the biological assay of cod liver oil for A is the criteria of A deficiency in experimental animals. None adopted thus far are 100 per cent perfect and are, at best, a matter of comparison.

The following standard has been recommended for adoption.

The new U S P XI vitamin A units are to be identical with the international units. The minimum vitamin A standard for U S P XI cod liver oil shall be not less than 600 international units.

The study of vitamin D has led to the recommendation that its potency in cod liver oil should also be expressed in terms of units. A unit is to be defined as the minimum average daily amount of cod liver oil required to produce a continuous narrow line across the metaphysis of a leg bone in four out of six rats in each group prepared under conditions specified for the assay.

It is well known that cod liver oil shows much less variation in its vitamin D potency than it does in vitamin A content. Notwithstanding this relative uniformity the British Medical Research Council has recommended the adoption of a standard ergosterol solution to serve as a measure for vitamin D potency of substances containing or claiming to contain this vitamin. This ergosterol was prepared from yeast by drying and dissolving in alcohol and subjecting the end product to irradiation from a mercury arc lamp. It was found that such a preparation was soluble in olive oil and retained its potency unchanged for as long as two years if kept below 0° C. The British Medical Research Council has recommended that the potency of this antirachitic substance be measured in terms of units and that either the roentgen-ray, "Line Test" method or chemical analysis of bones of experimental animals be used in estimation of vitamin D.

The Council defines the unit of vitamin D "as the antirachitic potency of a quantity of irradiated ergosterol corresponding to 0.0001 mg. of the ergosterol used in its production." One cc. of their standard solution, therefore, represents 1000 units of vitamin D activity.

The chief commercial supply of vitamin D in this country comes from irradiated ergosterol. Through the Council on Chemistry and Pharmacy of the American Medical Association this substance has come to be known as Viosterol. It is dispensed in a vegetable oil and is about one hundred thousand times as potent as an antirachitic as cod liver oil.

The Special Committee of the U S P XI has recommended that the minimum vitamin D standard for the U S P XI cod liver oil shall be not less than 85 international units.

Latterly much discussion has accumulated in the files of the Revision Committee concerning the definition of cod liver oil. A three-cornered discussion has just been concluded the participants being the officials of the Bureau of Fisheries, the Food and Drug Administration and the Sub-

Committee 8, of the Revision Committee U S P XI The point at issue was whether cod liver oil should be defined in the interim revision text as "the fixed oil obtained from fresh livers of *Gadus morrhua* Linne and of other species of *Gadus*" or "other species of the family Gadidae"

To the average physician it might seem a mere peccadillo whether the oil he prescribes for Junior sprang from the royal "species of *Gadus*" or emanated from the plebeian "family Gadidae" No doubt even Junior would be disdainful as to the source of his daily vitamin A, paraphrasing Shakespeare in asserting that "Cod liver oil from any other source would smell as malodorously" In this discussion commercial interests, as usual, took a hand The total domestic consumption of cod liver oil is nearly five million gallons, an average of two-thirds of a pint for each man, woman and child in the United States and her colonial possessions¹ Ninety-four per cent of this oleaginous river flows into the States from foreign countries, two countries, Norway and Newfoundland, supply 72 per cent of our imported oil These countries restrict the source of the oil to the genus *Gadus* To them the family Gadidae is anathema

To the Revision Committee the vitamin content and the esthetic qualities of the oil must be assured—the rest is twiddledee or tweedledum

COLOR STANDARDIZATION

Color, at first thought, appears simple and elemental White light passed through a prism and projected on a screen produces a band of light called a spectrum This spectrum presents a range of colors with violet at one end and red at the other, while indigo, blue, green, yellow and orange lie between, in the order named The shades between these primary colors which the eye can recognize and name are a bit limited, they are estimated at from three to 130

The U S P X used 287 different color names The importance of a color standard is recognized by the fact that these color names are used more than 2400 times in the book During the 10 year period following the last revision some research study was authorized by the Board of Trustees The result of that study was a very instructive color exhibit by the Committee at the Pharmacopoeial Convention May 13, 1930 During the session of the Convention the first Color Conference was held and more than 100 experts participated in the work of establishing workable standards for color estimation and uniformity in nomenclature Out of this Conference developed an "Inter-Society Color Council," to which representatives were accredited to chemical, architectural, physical, optical, engineering, pulp and paper, painters and decorators and motion picture societies More than a score of private individuals interested in color description and specification also participated

While the United States Pharmacopoeia initiated this study, it is evident that no marked changes in nomenclature could be made without the co-

operation of the many diverse interests of art, science and industry. In short, in the language of the Chairman, the definitions on limitations of color names should be "so accurate that science will accept them, so broad that science, art and industry can use them, so popular that the public can understand them."

The Pharmacopoeia is interested in two primary color problems, (a) the scientific standardization of color names, (b) the background color of "poison" labels. Experts are now at work checking the color names used in the coming text of the U. S. P. XI, correlating it with the color nomenclature being studied by the Council as a whole. This accomplishment will make the U. S. P. XI the first scientific publication to carry a color nomenclature based on a scientific foundation.

PERCENTAGE SOLUTIONS

When a physician writes a prescription for a preparation in solution in a given per cent he thinks he has given the pharmacist as specific directions as are necessary. As a matter of fact, the pharmacist recognizes that the term *per cent* has different meanings when used under varying conditions. He wonders if the physician means the sum of the percentages of the ingredients or the composition in terms of the finished product. The physician probably thinks, as a matter of mathematics, that the sum of percentages of ingredients means 100. The pharmacist remembers that a 10 per cent solution of sodium chloride may contain 95 per cent of water. Again, the physician writes for a "saturated solution" of potassium iodide and later the same order is written for sodium iodide. When the patient takes 30 drops of the first he is taking a solution containing 103 per cent of potassium iodide, while in the latter prescription there is 120 per cent of sodium iodide.

To obviate some of the uncertainties in prescription work it is proposed to carry under the caption, "General Notices" of the forthcoming Pharmacopoeia a statement somewhat as follows:

Per cent weight in weight to be expressed by the symbol W/W and means the number of grams of an active ingredient in 100 grams of the solution.

Per cent weight in volume to be expressed by the symbol W/V and means the number of grams of an active ingredient in 100 cubic centimeters of the solution.

Per cent volume in volume to be expressed by the symbol V/V and means the number of cubic centimeters of an active ingredient in 100 cubic centimeters of the solution.

That the expression per cent when used without qualification is to be interpreted as meaning for solution of solids in liquids, per cent, weight in volume, for solution of liquids in liquids, per cent, volume in volume, and for solutions of gases in liquids, per cent, weight in volume.

These terms are equally applicable to the metric and apothecaries' systems, e. g., a 1 per cent solution prepared under the metric system would contain one gram of a solid or one cubic centimeter of a liquid in enough of the

solvent to bulk 100 cubic centimeters of the finished product When prepared under the apothecaries' system 4.6 grains of a solid or 4.8 minims of a liquid in enough of the solvent to bulk one fluid ounce of the solution

Of course, in pure science percentage composition tables are expressed in terms of per cent by weight It is not common practice, however, in the United States to weigh liquids Some sanction to the proposed recognition in the U. S. P. XI may be found in the recommendation for adoption by all State Boards of Pharmacy of such a method by the National Association of Boards of Pharmacy, the adoption of such a method by the Conference of Pharmacy Teachers of the American Association of Pharmacy Colleges, the definition of percentage solutions and acceptance of the metric W/V solution in the book, "Useful Drugs," published by the American Medical Association for the guidance of faculties of medical schools and State Medical Examining Boards It may be further noted that the British Pharmacopoeia of 1932 introduced a similar statement under the heading, "General Notices," in an effort to establish uniformity in practice The introduction of such a statement as proposed into the U. S. P. XI will give official sanction to the metric W/V basis for making percentage solutions and make prescribing more definitely uniform

EDITORIAL

CHEMICAL FACTORS IN THE BEHAVIOR OF THE VEGETATIVE NERVOUS SYSTEM

WITHIN the past decade a new concept of the method of transmission of the effects of nerve impulses has developed. Dale recently has summarized the contributions and development of knowledge in this field. The first suggestion that a chemical agent acted as an intermediary between nerve stimulation and effector response was made by Elliot in 1904. After noting the similarity between the action of epinephrine and the stimulation of sympathetic nerves, he postulated that sympathetic nerve fibers liberated epinephrine at their endings, the epinephrine, he implied, might be the chemical intermediary between nerve impulse and effector response. Dixon was the first to suggest that the parasympathetic nerves might also release a chemical substance at their termination. The lucid experiments of Otto Loewi, in 1921, demonstrated for the first time the tenability of the foregoing hypothesis. He showed that the vagus nerve of the frog produced its effects on the heart by liberating an inhibitor substance which he termed "Vagus Stoffe". The fluid obtained from such a heart could be transferred to another heart, and again would exhibit an inhibitory or vagus effect. Loewi found this inhibitor or vagus substance corresponded to acetylcholine by all known tests.

The investigation of the part played in physiology by this derivative of choline forms an interesting chapter in medical research. Acetylcholine was synthesized by Baeyer in 1867, and its intense physiologic properties were discovered by Hunt and Taveau in 1906. It was not until 1914, however, that it was known to occur in nature, when Dale found it present in a sample of ergot. At this time Dale noted the remarkable similarity between the action of this substance and the effect of stimulation of the parasympathetic nerves. Acetylcholine causes inhibition of the heart, increase in intestinal tonus, and dilation of small arterioles. These actions can be abolished by atropine. It also has a third type of effect similar to nicotine, that is, there is a rise in blood pressure which is presumably due to stimulation of sympathetic ganglia, together with liberation of epinephrine.

Acetylcholine was first isolated from the animal body in 1929 by Dudley and Dale, who found it in extracts of the spleen of the ox. Recently, Chang and Gaddum have found it present in large amounts in the placenta of women. In an analysis of various body tissues they found the largest amount of "acetylcholine equivalent" in those tissues, the activity of which is controlled by the parasympathetic nerves.

It is almost certain at present that acetylcholine is the chemical transmitter of parasympathetic effects. Englehardt obtained a substance after reflex production of the autonomic actions of the third cranial nerve, which was similar to Loewi's "vagus substance" and presumably was acetylcholine.

Similar results have been obtained from stimulation of the chorda tympani nerve. Dale and Feldberg collected the substance released in the wall of the dog's stomach after stimulation of the vagus nerves and found it to correspond entirely to acetylcholine.

The fact that stimulation of the sympathetic nerves released a chemical substance was also first demonstrated by Loewi. The vagus nerve in the frog contains some sympathetic fibers, and at times stimulation caused acceleration of the heart. In these instances he found that the fluid from the heart transmitted an accelerator or epinephrine-like effect to another heart. Cannon and his coworkers recently have shown that, in a suprarenalectomized animal, stimulation of the lower end of the sympathetic chain caused release into the blood of a substance producing sympathetic stimulation in other organs. This substance closely resembles epinephrine. Cannon has called this substance sympathin and has expressed the belief that it is not identical with epinephrine. He stated that there are two types of sympathin: (1) Sympathin E, given off by smooth muscle which is stimulated to contract by sympathetic impulses and (2) Sympathin I, given off by smooth muscle which is inhibited by such impulses. Bacq has demonstrated that stimulation of the cervical sympathetic nerves causes release of a substance in the aqueous humor which is either epinephrine or closely related to it.

All evidence to date, then, points to acetylcholine as the chemical transmitter of parasympathetic effects and epinephrine or a closely related substance of sympathetic action. There are outstanding exceptions to this rule, so that Dale suggested the terms "cholinergic" and "adrenergic" to indicate the function of nerve fibers. The sweat glands of the cat and of the hand of man, although supplied by fibers of sympathetic ganglion cells, respond but little to epinephrine, but are stimulated to secretion by pilocarpine or acetylcholine. Feldberg and Dale showed that stimulation of the sympathetic nerve supply to the foot of the cat caused liberation of acetylcholine. These fibers are therefore cholinergic.

The mode of transmission of nerve impulses across synapses has never been well understood, nor has it been explained how the nerve impulse passes from motor end plates to voluntary muscle. Recent evidence indicates that acetylcholine may intervene in both these situations. Kibjakow perfused the superior cervical ganglion of a cat, and found that something appeared in the fluid after stimulation of preganglionic nerves which on reinjection acted as a stimulus to activity. In other words, impulses are transmitted across a synapse by release of this substance. Feldberg and Gaddum, using the same technic, showed that the substance was apparently acetylcholine. It is interesting to note that stimulation of the splanchnic nerve to the suprarenal gland caused acetylcholine to appear in the blood of the suprarenal vein (Feldberg and Minz).

Acetylcholine is known to stimulate certain voluntary skeletal muscles in lower vertebrates and in mammals after the motor nerves have degen-

erated Recently, Feldberg and Dale have shown that stimulation of the hypoglossal nerve (after causing the sympathetic fibers normally present in it to degenerate) results in the formation of acetylcholine

It seems probable from the mass of evidence accumulating that chemical substances are released at all cytoneural junctures in the periphery to act as transmitters of nerve impulses Perhaps the same is true of synapses in the central nervous system Dikshit recently showed that a small amount of acetylcholine injected into the intraventricular fluid caused effects on respiratory activity similar to central stimulation of the vagus nerve

The discovery of the substances concerned in chemical transmission of nerve impulses opens up a new field for clinical research and therapeutics Acetylcholine itself is not useful clinically, as its action is too evanescent, and it must be given intravenously Recently new derivatives of choline have been synthesized One of them, acetyl- β -methylcholine, can be given orally and subcutaneously, its effects are less transitory, and it may be useful in certain diseases or disturbances of cholinergic nerves This concept of the behavior of nervous activity will help to clarify many puzzling phenomena observed in disorders affecting the vegetative nervous system

G A G

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REVIEWS

Acute Intestinal Obstruction By MONROE A McIVER, M D, Surgeon-in-Chief, Mary Imogene Bassett Hospital, Cooperstown, N Y 430 pages, 19 × 26.5 cm Paul B Hoeber, Inc, New York City 1934 Price, \$7.50

This monograph contains a very complete presentation of both the experimental work upon the consequences of acute obstruction, and the clinical aspects of this condition. The toxic, bacterial and splanchnic paresis theories are discussed and full references given to the literature. The clinical and pathological varieties of obstruction are described in detail. There is a very complete and valuable presentation of the problems associated with diagnosis and treatment. The investigator who is interested in this field and the practicing clinician will find this a helpful study of an important subject.

C H

The Medical and Orthopaedic Management of Chronic Arthritis By RALPH PEMBERTON and ROBERT B OSGOOD vii + 403 pages, 15 × 22 cm The Macmillan Company, New York 1934 Price, \$5.00

In this book Pemberton and Osgood have quite thoroughly covered the single type of arthritis known as Chronic Arthritis. Of the 14 chapters, six are devoted to the various phases of treatment, this is as it should be since "what to do" is more important to the patient than "what is it?" Encouragement is given to the patient rather than the opposite which is so often the case.

Chapter II presents the evolution of the terms of classification since 1857 and ends by offering the two most commonly accepted division titles, atrophic and hypertrophic. These names are both descriptive and simple and they avoid the weakness of the so often attempted, but rarely completed, efforts to classify strictly according to etiology, or pathology, etc.

The pathological and physiological phases of the subject are fully covered. Unfortunately the physiology is not as clearly understood as is the pathology due to the differences in availability of material, etc., but a complete analysis of the many theories is presented with a brief explanation relative to the authors' views on each phase.

The six chapters on treatment are quite extensive and cover practically all available methods for the alleviation of the disease. The value of each method is weighed on the scales of the authors' experience which is extensive. Emphasis is placed upon the fact that no cure-all is now known for chronic arthritis and that the results of treatment are dependent upon slow, painstaking, and consistent work with one or more methods. Strength is placed upon the upbuilding of the body in general and the care of all system functions, especially posture and bodily activities, and the gastrointestinal tract.

This book offers a complete review of the subject of chronic arthritis from as nearly an unbiased and neutral standpoint as is possible. At times the discussion seems a trifle diffuse. Due emphasis is placed upon the necessity of a minutely careful survey of the individual as a whole, weighing the relative values of the abnormalities discovered. It is pointed out that in most cases improvement will be attained if a careful and thorough routine is followed. The vital importance of early diagnosis and of early treatment is stressed. In the convincing presentation of the foregoing fundamental principles lies perhaps the chief value of this interesting monograph.

A V

An Introduction to Sex Education By WINIFRED V RICHMOND, Ph D, Psychologist, St Elizabeth's Hospital, Washington, D C 299 pages, 14 × 21 cm Farrar and Rinehart, Inc, New York City 1934 Price, \$2 50

This is the third book that Dr Richmond has written on the subject of sex education, yet there is very little that is repetition in this series. This latest book is an attempt to clarify the thinking on the whole subject and to give a concise and scientific discussion of the problem. Although Dr Richmond is a psychologist, she has had a broad experience with abnormal as well as normal psychology, and has been closely in association with the medical group at the federal hospital, and it is evident from her references that she has widely read the medical literature on the subject under consideration.

In these chapters she discusses general biology, biology of reproduction in man, sex in primitive society, marriage and the family, psychology of sex, specific problems preventing proper adjustment in sex, and problems complicating marriage. In her final chapter she very sanely presents a program of education. The physician will find this is a book that he can safely recommend to his patients without the fear of creating morbidity.

J L McC

Clio Medica German Medicine By W HABERLING, M D, translated by JULES FREUND, M D 160 pages, 11 × 17 cm Paul B Hoeber, Inc, New York City 1934 Price, \$1 50

The Clio series of small volumes on various phases of medical history has recently had two new volumes added. The one under consideration, by the erudite professor of medical history at Dusseldorf, is a masterly presentation in small space of the achievements of German and Austrian physicians in the fields of medicine, surgery and the specialties. The amount of knowledge added by the Teutons is indeed remarkable. One need only glance at the names Paracelsus, Friedrich Hoffman, Stahl, Haller, van Swieten, Johannes Muller, Theodor Schwann, Virchow, Koch, von Behring, Ehrlich, Rontgen, Pettenkoffer, von Graefe—to mention just a few of the outstanding ones.

The growth of medicine in Germanic lands is traced from the crude beginning in the ancient times, through the middle ages and the fruitful eighteenth and nineteenth centuries down to the present much specialized age. Haberling misses the great contribution made unwittingly by Hahnemann, in that he showed us the natural history of disease uninfluenced by drugging and so eventually pointed the way to a more sane therapy. The editor of the series makes good the omission in a footnote.

This series of books which can be put in the pocket is a splendid undertaking and should do much to popularize the much neglected subject of the history of medicine, a full knowledge of which renders full of meaning the trends of medical thought as we see them today. This is a worthy companion to the preceding volumes.

J R

The Mother's Encyclopedia Edited by MARY E BUCHANAN, managing editor of *The Parents' Magazine*. Articles contributed by 130 authors. vii + 959 pages, 4 vols, 12 × 18 cm Home and School Book Service, The Parents' Publishing Assoc, Inc, New York City, N Y 1933

This encyclopedia is unique in that it is the first time that an attempt has been made to publish in book form a series of articles covering the whole field of child care from the parent's viewpoint. The editor of this four-volume set of books has gathered articles written by some of the foremost authorities in the field of child health and training, child psychology, nutrition, sex education, family relationships,

play and play equipment All the articles at one time appeared in *The Parents Magazine*, but these articles have been condensed and edited wherever necessary to bring them strictly up to date Cross references under every subject, sub-titles on nearly every page and a voluminous index in the final volume make it possible to find quickly any subject under consideration

Of the 130 men and women who have contributed to this encyclopedia, 31 are physicians The articles are written in a sane and scientific manner without the usual hodge-podge that is so frequently found in books on health written for the laity There is nothing said that would lead patients to self-medication, as is the usual result of lay reading of medical articles Physical health is fully discussed, but the largest number of pages is taken up in the discussion of child guidance and the emotional development of the individual

At the end of the encyclopedia is a table of contents grouped by age interests infancy, pre-school age, school age, adolescence, all ages and parenthood Under infancy are such articles as Bathing the Baby, Weaning the Baby, Respiratory Diseases, and Fear In the second grouping are such articles as Enuresis, Habit Training, Night Terrors, Sleep Routine, Thumbsucking, and Answering Children's Questions In the school age group some of the articles are How to Choose the Right School, Physical Growth, Home Study, Creative Education, and Social Training Under adolescence are such subjects as The Foods Needed, Friction in the Family, Cosmetics, Delinquency, Scouting, Nervous Breakdowns, Love, and Vocational Guidance Some of the other titles picked at random are Budgeting the Family, Convalescent Occupations, Adoption, How Big Should a Family Be, Maternity Clothes, Eye Protection, Divorce, Dancing, Masturbation, Obedience, and Health Guidance

Since most physicians are parents and as puzzled over the problems of bringing up children as their lay patients, the physician will find considerable help in this encyclopedia as well as a good deal of interesting reading, which will give him a better insight into the problems he is so frequently consulted about

J L McC

Klassifikation der Schizomyceten (Bakterien) Versuch einer wissenschaftlichen Klassifikation der Bakterien auf botanischer Grundlage By PROF DR ERNST PRIBRAM, D Z Professor für Bakteriologie und Präventiv-Medizin an der Loyola University, School of Medicine, Chicago, Illinois Paper, 143 pages Franz Deuticke, Leipzig and Vienna 1933

The investigators to whom bacteriology owes its rapid development during the latter part of the last century were untrained in taxonomy and the rules of biological nomenclature The results were quite naturally the frequent adoption of faulty names for bacteria and the lack of an adequate and satisfactory system of classification A number of attempts have since been made to correct these errors but the suggested changes have not had official sanction On the other hand these newer names and more recent systems have been used by some authors, while others retain the older terminology and classification This has led inevitably to a condition bordering on chaos in the fields of nomenclature and taxonomy Pribram now presents a new system This monograph represents the work and experience of some 20 years and offers a classification differing materially from that suggested in 1929 by the same author In his terminology he follows quite strictly the biological code and also leans heavily on the suggestions offered by the Committee of the Society of American Bacteriologists

In his classification the author makes use of the work of his predecessors but has deviated from their systems in many ways He has attempted to meet the requirements of exactness and elasticity, the latter by the use very largely of only one attribute as a characteristic of a group and by making subdivisions for each character

This elasticity is wanting in former classifications which thus allow no place for transitional forms or for new hitherto unknown species

The author's monograph is in two parts, preceded by a tabular synopsis of schizomycetes. The first explains this table and discusses the nomenclature and classification. The second part is devoted to the classification of the cultures of bacteria at present in the Kral collection in Vienna. There is an excellent index and an extensive bibliography.

Pribram divides the bacteria into three subclasses: algobacteria, eubacteria, and mycobacteria. The algobacteria include those forms adapted to life in water, and some of the parasitic and pathogenic microorganisms. This subclass contains organisms transitional between bacteria and algae, and others bridging the gap between the bacteria and the protozoa. The algobacteria are arranged in their various families distributed among four orders. The eubacteria include most of the "true bacteria" not placed in the first subclass, they are arranged in five families under two orders. The mycobacteria are subdivided into two orders. One of these contains the aerobic and the anaerobic, spore-bearing bacilli, each in a separate family, and the other, distributed between two families, most of the bacteria recently grouped in the order actinomycetales by Bergey and others.

In comparing the classification adopted by Pribram with some of the other modern systems we find many divergencies. Thus, whereas in the latter, the sulphur bacteria are placed in a single order, here they are distributed among several orders of the algobacteria. Again, the "slime bacteria" are generally arranged in a single family but are here placed among the algobacteria in two families. Indeed, one of the genera (*Myxococcus*) is found in the same family with *Vibrio cholerae* and *Ps. aeruginosa* (*B. pyocyaneus*), a rather startling juxtaposition. Also the spirochetes are put in an order of the algobacteria containing some of the sulphur bacteria, although in a different family, it is true. The cocci, which heretofore have all been classified in a single family, are found distributed among several families of algobacteria and eubacteria. Whereas most of them are classed in the first of these groups, the streptococci, including the pneumococcus, are discovered in the same order, but in a different family, of eubacteria as the proteus and acidophilus groups. The genus *Neisseria*, however, because of its strict adaptation to the animal organism, is placed in a family of the eubacteria with the brucella, the hemorrhagic septicemia, and the hemoglobinophilic groups. The classification of the spore-bearing bacteria removes them further from the other "true bacteria" and brings them into closer relationship with the tubercle bacillus, the diphtheria bacillus, and the actinomycetes than is usual. Also in the arrangement of the genera of actinomycetales in families, Pribram differs from the Committee of the Society of American Bacteriologists and from Bergey. These citations give some indication of the degree to which the classification offered in this monograph diverges from former systems. The author publishes his work in the full knowledge that it will call forth much opposition and criticism. May this discussion serve to stimulate interest in the solution of the problems and hasten the day of the adoption of a definitive system of taxonomy.

F W H

COLLEGE NEWS NOTES

Acknowledgment is made of the following gifts to the College Library of publications by members

Dr Elliott P Joslin (Fellow), Boston, Mass—1 book, "Diabetic Manual"

Dr Samuel M Feinberg (Fellow), Chicago, Ill—1 book, "Allergy in General Practice"

Dr Joseph R Darnall (Fellow), Ancon, C Z—2 reprints

Dr C Glenville Giddings (Fellow), Atlanta, Ga—1 reprint

Dr Arthur H Jackson (Associate), Washington, Conn—2 reprints

Dr Henry S Houghton (Fellow), Chicago, Ill, has resigned as associate dean of the Division of Biological Sciences and director of the University Clinics, University of Chicago, to become advisory representative of the China Medical Board, beginning January 1, 1935 Dr Houghton was formerly dean of the University of Iowa College of Medicine The China Medical Board, as an agency of the Rockefeller Foundation, owns and supports the Peiping Union Medical College

Dr Phillipp Schonwald (Fellow), Seattle, Wash, addressed the Rocky Mountain Tuberculosis Conference, Colorado Springs, Colo, September 17 to 19, on "A Modification of the Blood Sedimentation Test in Tuberculosis"

Dr Harold S Davidson (Fellow), Atlantic City, N J, has been selected as General Chairman for the annual meeting of the American Therapeutic Society, meeting in Atlantic City, June 7 to 8, 1935

Dr Zacharias Bercovitz (Associate), formerly of the Pyengyang Union Christian Hospital, Pyengyang, Chosen, Korea, has completed some postgraduate work at the London School of Tropical Medicine and announces he will resume practice at 889 Lexington Avenue, New York City Dr Bercovitz has been appointed to the clinic staff in gastro-enterology of the New York Post Graduate Medical School and Hospital

Dr Seale Harris, Jr (Associate), Nashville, Tenn, has been promoted to associate professor of medicine at the Vanderbilt University School of Medicine

Dr Rock Slevster (Fellow), Wauwatosa, Wis, was the recipient of the gold seal of the State Medical Society of Wisconsin at their annual dinner, September 13 Dr Slevster is editor of the state society's journal He was formerly president and secretary of the society, and he is now vice-chairman of the Board of Trustees of the American Medical Association

At the formal opening of the new headquarters for the Lilly Research Laboratories, Indianapolis, on October 11, the following Fellows of the College were speakers Sir Frederick Banting, Toronto, Dr Elliott P Joslin, Boston, and Dr George R Minot, Boston

Dr David P Barr (Fellow), Busch professor of medicine, Washington University School of Medicine, St Louis, delivered a series of three lectures before the Honolulu County Medical Society, September 12 to 14. His titles were "The Pituitary Gland," "Hypoglycemia and Related Conditions" and "Parathyroid Gland and Calcium Metabolism"

Dr William B Castle (Fellow), Boston, Mass, gave the first Harvey lecture this year, October 18, at the New York Academy of Medicine, "The Etiology of Pernicious and Related Macrocytic Anemias"

The Philadelphia General Hospital, under the chairmanship of Dr Russell S Boles (Fellow), has inaugurated a series of Saturday morning clinics from 11 to 1 o'clock, covering a broad variety of medical and surgical subjects, with demonstration of cases, but without operative clinics. These clinics are conducted in the interests of the general practitioner and are open to the medical profession and to medical students. At the first clinics, October 6, Dr David Riesman (Fellow), Dr Thomas M McMillan (Fellow) discussed "Recognition of the Failing Heart," Dr Edward A Strecker (Fellow) presented a clinic on "The Neuroses as Encountered by the General Practitioner." On October 13, Dr Arthur C Morgan (Fellow) presented a clinic on "Physical Signs of Pulmonary Tuberculosis." On October 20, Dr Daniel J McCarthy (Fellow) presented a clinic on "The Cerebral Apoplexies." On October 27, Dr Robert G Torrey (Fellow) presented a clinic on "Rheumatic Heart Disease"

RESEARCH FELLOWSHIP OF THE AMERICAN COLLEGE OF PHYSICIANS

At a meeting of the Board of Regents at Chicago, Ill, April 15, 1934, the following resolution was adopted:

"Resolved, that the Board of Regents establish a Fellowship in the amount of \$1,800.00 to be known as the 'Research Fellowship of the American College of Physicians' and to be awarded each year on the recommendation of the Committee and the approval of the Board of Regents"

The Committee on Awards, appointed by the Board of Regents, is as follows:

David P Barr, St Louis, Chairman
Arthur R Elliott, Chicago
James H Means, Boston
William J Kerr, San Francisco
O H Perry Pepper, Philadelphia

The Committee proceeded immediately after the adoption of the resolution to obtain applications for this Fellowship. The names of a number of individuals applying for similar fellowships were obtained from the National Research Council, and from other sources. After reviewing these candidates' records and communicating with each, the names of two were selected by the Committee and presented to the Board of Regents of the American College of Physicians for final selection.

Dr Frederick Kellogg, of San Francisco, was awarded the Fellowship, and his work began on September 15. Dr Kellogg obtained his A B degree at Stanford University in 1927, and his degree in medicine at Harvard University Medical School in 1931. He then worked for a period of time with Dr Paul White, until he returned to California to take up clinical research work at the University of California Hospital. He has published a number of articles chiefly on cardiology and on anemia.

The problem Dr Kellogg intends to follow out during the coming year on the Fellowship of the American College of Physicians is a study of hemoglobin regeneration and the relative effectiveness of various dietary factors before and after gastrectomy. This work will be done in association with Dr Stacy R Mettier (Fellow). Dr Kellogg also hopes to pursue some work on phonocardiography with Dr William J Kerr (Fellow).

It is not too early to point out that this same Fellowship will be open again next year, and that applications may be filed at any time through the Executive Offices of the College.

FELLOWSHIP INSIGNIA FOR ACADEMIC GOWN

Occasional queries from manufacturers of academic gowns indicate some Fellows of the American College of Physicians are not familiar with the official method of indicating Fellowship or Mastership in academic dress.

There is no official gown for the American College of Physicians, but a special insignia to be attached to any regular or special gown a member may already have. For Fellowship, the insignia is a cross of the shape of that of the Key of the College, three inches in height, of green velvet, with the seal of the College stitched in solid gold braid, to be attached and worn on the right side of the academic gown. For Mastership, the insignia is a similar cross, except of gold cloth with green braid.

These insignia may be obtained, ready for stitching to the gown, through the Executive Offices of the College, 133-135 S 36th St, Philadelphia, Pa.

CIRCULATION OF ANNALS OF INTERNAL MEDICINE

In compliance with the regulations of the Code Authority for the Periodical Publishing and Printing Industry (A-3), the American College of Physicians, publishers of the ANNALS OF INTERNAL MEDICINE, presents the following statement concerning the circulation of said journal for the period beginning January, 1934, and ending June, 1934.

Average gross circulation —3,197

Average net paid circulation—3,074

Subscribed and sworn to by E. R. LOVELAND, Executive Secretary of the American College of Physicians, this eighth day of October, 1934.

My commission expires April 8, 1937
(SEAL)

B. M. SNOVER,
Notary Public

OBITUARIES

DR GEORGE WALTER HOLDEN

1866-1934

By the death of Dr George Walter Holden, of Denver, from coronary thrombosis on July 11, 1934, Colorado lost one of her ablest and best known physicians. Born in Barre, Mass., September 17, 1866, his early education was obtained in the Barre Academy, and in the Mount Herman Academy at Northfield, Mass. Following a business course Dr Holden's artistic nature craved a medical career and when he had saved enough money he entered the University of Vermont at the age of 26, graduating in medicine in 1895. After hospital experience in Boston a general practice was undertaken in North Brookfield, Mass. He was overtaken with pulmonary tuberculosis and came to Colorado where his fame was made as a specialist in that disease.

When Mr Lawrence C Phipps, former United States Senator from Colorado, conceived and built the Agnes Memorial Sanatorium for Tuberculosis, his family physician, Dr Holden, was appointed Superintendent and Medical Director, which position he held from 1904 to 1932 when the institution closed. While Dr Holden's ability as a well-trained physician was thoroughly tested in this long and faithful service, a marked administrative and disciplinarian capacity was developed which made the Agnes Memorial Sanatorium recognized as one of the best sanatoria in the country.

Dr Holden was a member of the American Clinical and Climatological Association, the American Hospital Association, the American Sanatorium Association, the American Public Health Association, the National Tuberculosis Association (Vice-President and Director), the Colorado Tuberculosis Association (President), the Denver Tuberculosis Society (President and Director), and the Colorado Hospital Association (Vice-President). Dr Holden was also a Fellow of the American Medical Association and of the American College of Physicians.

While not a frequent contributor to medical literature Dr Holden was interested in the investigation of such rare conditions as aspergillosis of the lungs. Dr Holden gave himself to such activities as the Child Research Council and possessed all the qualities of a true and earnest physician.

GERALD B WEBB, M D, F A C P,
Governor for Colorado

DR BENJAMIN GUTMANN

Dr Benjamin Gutmann (Fellow), 144 Livingston Avenue, New Brunswick, N J, died August 7, 1934, at the Middlesex Hospital after several months illness from bronchiogenic carcinoma.

Dr Gutmann was born at South Amboy, N J , December 29, 1877 He received his preliminary education from the schools of his native town and entered the Glenwood Military Academy, Matawan, N J , from which he graduated in 1893 He entered the Jefferson Medical College, Philadelphia, Pa , in 1893 and graduated in 1897 He returned to his native town, New Brunswick, and practiced general medicine until 1913 when he went abroad to study at Vienna and Berlin and returned again to resume his practice

In 1919 he did special work at Harvard University Graduate School and was at the Massachusetts General Hospital, Boston, and the Presbyterian Hospital, New York City Upon his return he limited his practice to Internal Medicine Dr Gutmann was Chief, Medical Service, Middlesex General Hospital, and St Peter's General Hospital, New Brunswick, at the time of his death

He was married to Marie Louise Fisher, daughter of Charles and Ella De Hart Fisher, November 15, 1904, and is survived by four daughters, Margaret, Elizabeth, Anne and Mrs Willard Potter

Dr Gutmann was a member of the Middlesex Medical Society, the New Jersey State Medical Society, the American Medical Association and a Fellow of the American College of Physicians since 1929 He was also a member of the Rutgers Medical Club, Anglo-American Society of Berlin, American Association of Vienna and the Academy of Medicine of Northern New Jersey

The profession and College have lost a worthy member

CLARENCE L ANDREWS, M D , F A C P ,
Governor for New Jersey

DR ISADORE D BRONFIN

1886-1934

Born in Russia in 1886, Dr Bronfin came to the United States in 1902 He was educated at the University of New York and graduated in medicine at the Long Island College Hospital in 1911 Developing pulmonary tuberculosis Dr Bronfin came to Colorado in 1920 and, as so many of his predecessors had done, took up the specialty of tuberculosis in which field he became a national authority Dr Bronfin became Superintendent of the Jewish Consumptive Relief Society and was appointed Medical Director of the National Jewish Hospital in 1927 Absorbed in his work and indefatigable in his efforts to help the tuberculous, his own affliction relapsed and his death occurred July 30, 1934, following a series of serious pulmonary hemorrhages Dr Bronfin was loved and respected by all the profession of Colorado He was a member of the faculty of the University of Colorado School of Medicine, and was a conscientious attendant of all medical society meetings Dr Bronfin is survived by his wife, Mrs Elizabeth Bronfin, and by two sons

GERALD B WEBB, M D , F A C P ,
Governor for Colorado

DR CURRAN POPE

Dr Curran Pope of Louisville, Kentucky, died September 21, 1934, at his home. He had been an Associate of the American College of Physicians since 1920. He was born in Louisville on November 12, 1866, and after graduating from public and high schools received his degree in Medicine from the University of Louisville Medical Department, 1889. He took postgraduate courses in New York, London, Paris, Vienna and Berlin, and became resident physician at the Central State Hospital in 1891. He was connected with the Hospital College of Medicine, the Louisville College of Medicine, Kentucky School of Medicine and the University of Louisville Medical Department during the years 1892 to 1910. He was very much interested in physiotherapy and, at the time of his death, was Director of the Pope Hospital in Louisville. He was a past President of the Ohio Valley Medical Association, Western Physical Therapy Association and the American College of Physical Therapy. He was the author of a book on "Practical Hydrotherapy" and several hundred articles and many editorials contributed to leading medical magazines of this country.

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ARTERIOLAR INFARCTION *

By J C MEAKINS, M D , F A C P , *Montreal, Quebec, Canada*

FOR want of a better title I have chosen the above, to include the hemorrhages into the skin, mucous membranes and viscera which are of such common occurrence in those pathological states where hypertension is a prominent feature. It may be taken at the present time that hypertension as a functional disturbance is dependent upon an increased peripheral resistance in the vascular system. There is considerable difference of opinion as to whether this increased resistance is a function of the whole arteriovascular tree including arteries, arterioles and arterial capillaries, or whether it is principally produced by a narrowing of the arteriolar bed with normal pressure in the arterial capillaries. For the present this discussion need not enter into our consideration.

That the functional disturbance which produces hypertension is more or less constant throughout the body is usually agreed, with the qualification that there are periodic fluctuations in the total effect and also isolated variations in tissues and organs from time to time. The principal pathological states with which hypertension is intimately associated might be stated as follows: (1) eclampsia, (2) acute hemorrhagic Bright's disease, (3) hyperpiesia, and (4) chronic hemorrhagic Bright's disease with nephrosclerosis. I have listed them in this order as it corresponds to the acuteness with which the hypertension develops.

There is general agreement that the original disturbance is due to some vaso-pressor action on the arterial system and not to an anatomical disturbance. The latter, however, in the last two groups may occur in time, more as a consequence rather than a cause of the functional disturbance. The anatomical changes can be best described as a hypertrophy of the muscular elements of the cardiovascular system, as shown by the increased volume of the myocardium and muscular coats of the arteries and arterioles. There is also a thickening of the arterial intima with narrowing of the lumen which in time may lead to a gradual obliteration of the smallest arteries, and changes in the parenchymatous architectural patterns. These anatomical changes are as a rule a function of time and severity of the pressor effect.

* Read at the Chicago meeting of the American College of Physicians, April 16, 1934.
From the Department of Medicine, McGill University Clinic, Royal Victoria Hospital, Montreal.

These changes are more or less uniform throughout, in distinction to the true degenerative arteriosclerotic process which is irregular and patchy and in itself is not necessarily associated with hypertension and seldom if ever produces it

In the past, hemorrhages accompanying hypertension were attributed to various "toxic" causes or to anatomical changes, the result of arterial damage. At the present time opinion tends more to the conception that they are a direct result of the general or local variations in the hypertensive state. The condition of the smaller arteries, arterioles, capillaries, venules and smaller veins can be studied in life by experimental methods in the skin and fundus oculi.

We are indebted to Richer and his coworkers¹ for their experimental studies of the circulatory movements in normal and abnormal states. They clearly demonstrated that under moderate stimulation—mechanical, chemical or bacterial—the smallest arteries contract, slowing the blood flow through them, and the capillaries and venules dilate. If the stimulus be sufficiently intense the proximal arteries contract to such a degree as to pro-



FIG 1 Mesentery of a rabbit stimulated with a suspension of *B. coli*, showing contracted arteriole and dilated venule with diapedesis and hemorrhage

duce closure Richer has given the term *peristasis* to the slowing of the stream and *stasis* to its complete stoppage But the condition is not fixed and varying degrees may be observed, and stasis is usually preceded by an extreme slowing which has been termed *prestasis*

In the stage of *prestasis* there is an out-flowing of the blood constituents from the capillaries and venules, and, depending upon the degree of *peristasis*, there may be exudates of plasma, leukocytes or finally erythrocytes In the extreme slowing, blood extravasation by diapedesis occurs, in other words, hemorrhages through vessels which are not ruptured When stasis or complete stoppage occurs, tissue necrosis (infarction) ensues unless collaterals are available This permeability of the capillaries and venules is enhanced by the local oxygen want produced by the slow circulation, and is in proportion to the degree and duration of the *peristasis* The principal features to be seen are the narrowed small arteries and arterioles with dilated and engorged capillaries, venules and smaller veins about which masses and collars of erythrocytes are seen to appear rapidly The extent of the hemorrhagic extravasation may be extreme, extending over large areas and producing extensive local destruction (Figure 1)

In pathological states similar phenomena may be observed Koch,² in Volhard's clinic, showed that following scarlet fever irregular elevations in blood pressure occur several days before the onset of the classical symptoms of nephritis With the increase in blood pressure there is a generalized constriction of the small arteries and arterioles, which can be studied in the skin and the retina It is at this time that hemorrhages appear in the skin, mucous membranes, retina and kidneys and probably other viscera as discovered at post mortem

A lucid and illuminating review of the changes in the retina in hypertensive conditions has recently been published by Elwyn³ In this he explains and interprets all the changes found in the retina in so-called nephritic retinitis on the experimental work of Richer and his coworkers It is the only interpretation at the present time which in any way approaches all the requirements

In acute nephritis and eclampsia with hypertension, the fundal lesions are not necessarily progressive but are variable and labile, varying in degree from day to day and being subject to pronounced and sudden changes

The arterial constriction occurs also in the brain and is responsible for the edema and focal hemorrhages (figure 2) which give rise to the cerebral symptoms, convulsive seizures and associated phenomena

It has already been stated that hemorrhages are a common occurrence in the hypertensive state Postmortem examinations show that no organ or tissues may be exempt However, particular attention has been focused upon certain sites because of the conspicuous disabilities which may ensue Melena, hematemesis, hematuria and purpura, do not lead to grave disabilities comparable to those which are met with when hemorrhagic extravasations occur in the fundus oculi, brain, and myocardium



FIG 2 Microscopic section of the brain from a case of cerebral hemorrhage in a man aged 24 with hyperpiesia. It shows continuous perivascular "collar" hemorrhage with extensive erythrodiapedesis

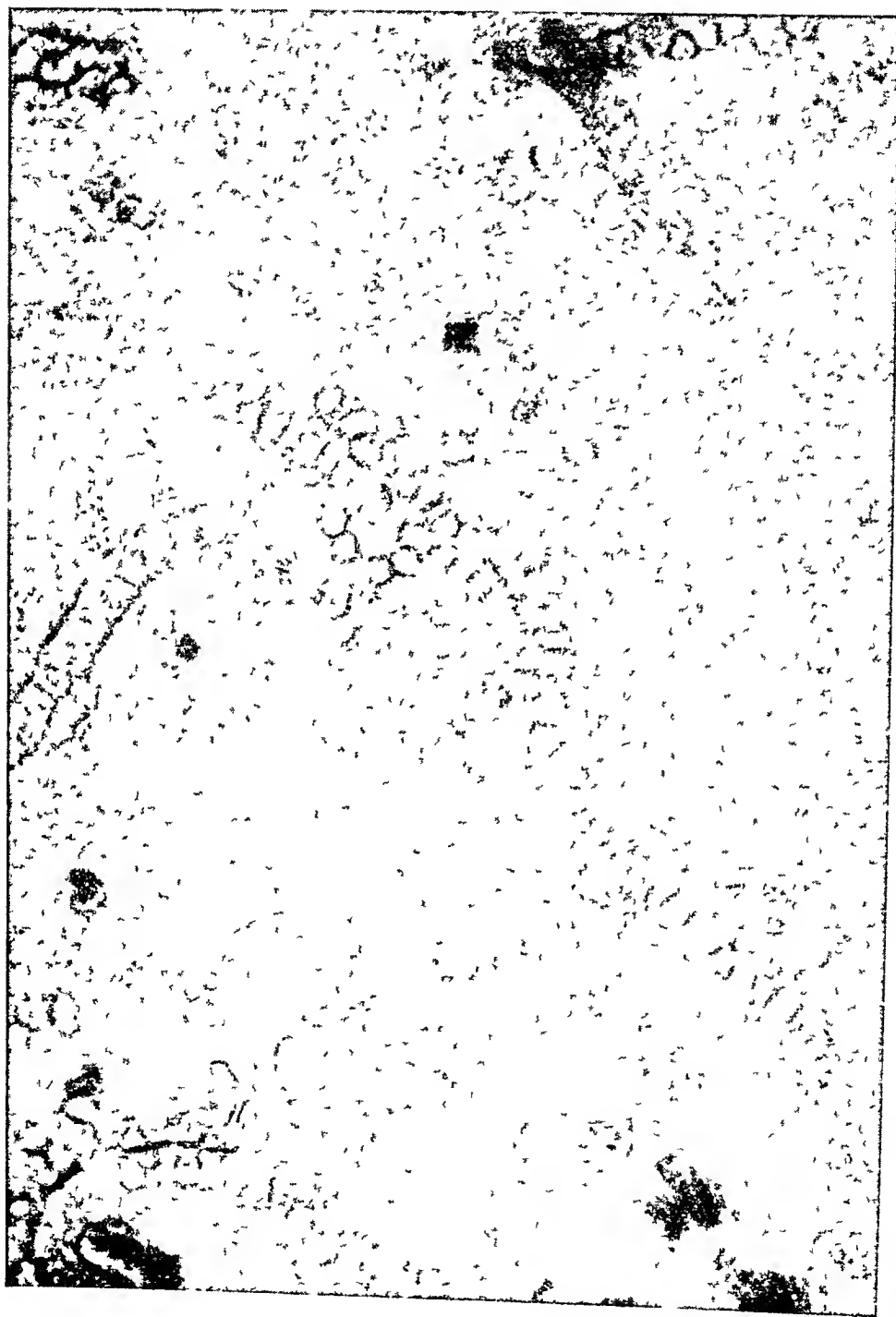


FIG. 3 Microscopic section of the brain from a case of cerebral hemorrhage in a woman aged 31 with hypertension. It shows erythrodiapedesis surrounding a capillary and in the lower right corner a venule filled with agglutinated erythrocytes producing thrombosis with but little erythrodiapedesis.

Cerebral hemorrhage is usually conceived to be due to an actual rupture of a vessel, although in a search of the literature actual proof of such in all but a small percentage of cases is sadly lacking. In fact, the majority of evidence would indicate that such is not the case, and experimental evidence would strongly point to stasis and diapedesis as being the principal cause, particularly when hypertension is present. Indeed, Virchow was strongly in favor of this interpretation more than 75 years ago.

On analyzing cases of cerebral hemorrhage certain rather striking features are revealed. Over a period of five years, 37 cases of cerebral hemorrhage, exclusive of those with a syphilitic or traumatic history, have been analyzed. Three of these were cases of eclampsia, 23 had hypertension with a diastolic pressure of over 110 mm of mercury. The average systolic pressure was 224 mm, the average diastolic pressure, 130. Sixteen were males and seven females, and the average age was 48, the oldest being



FIG 4 Macroscopic section of brain from a young woman aged 22 with eclampsia and hypertension. It shows two gross and numerous minute hemorrhages.

62 years of age. The remaining 11 cases had a diastolic pressure of 90 mm of mercury, the average systolic pressure being 143 mm and the average diastolic being 78 mm. Eight were males and three females; the average age was 73 years (58 to 85). In the hypertensive group, hemorrhages varied from small petechial extravasations to mass and widely destructive lesions. Not only were they frequently multiple in the brain (figures 4 and 5), but hemorrhagic extravasations were always found in other viscera—such as the gall-bladder, stomach, duodenum, ileum, kidney (figure 6), renal pelvis, and bladder—if thoroughly examined. This was also true in the cases of eclampsia. In all of these hemorrhagic states in which detailed examinations of the fundi were recorded, retinitis was found. In the cases with low or normal blood pressure, hemorrhages were always isolated in the brain and were single. Visceral scarring suggestive of old vascular lesions was sometimes

FIG 2 Microscopic section of brain from a young woman aged 22 with eclampsia. It shows confluent hemorrhages.

In none of these cases was there retinitis, although all revealed arteriosclerosis of the retinal arteries without the so-called loss of compensation in the veins

The hemorrhagic extravasations in hyperpiesia and eclampsia are practically identical with those produced by local irritations, as was brilliantly investigated by Richer and his coworkers (figure 1) In the experimental states, if the stasis was complete, hemorrhagic extravasations did not occur, but agglutination of the erythrocytes occurred within the capillary or venule, leading to thrombosis (figure 3) This has also been demonstrable in cases of hyperpiesia and eclampsia Anatomical occlusion of an artery or arteriole, due to a degenerative arteriosclerosis, may also produce complete stasis and thrombosis or rupture of such a vessel may occur, but, as already pointed out, this is usually a local lesion, although repeated accidents may occur There is not, however, the labile, fluctuating, systemic disturbance present which is so characteristic of the functional hypertensive states

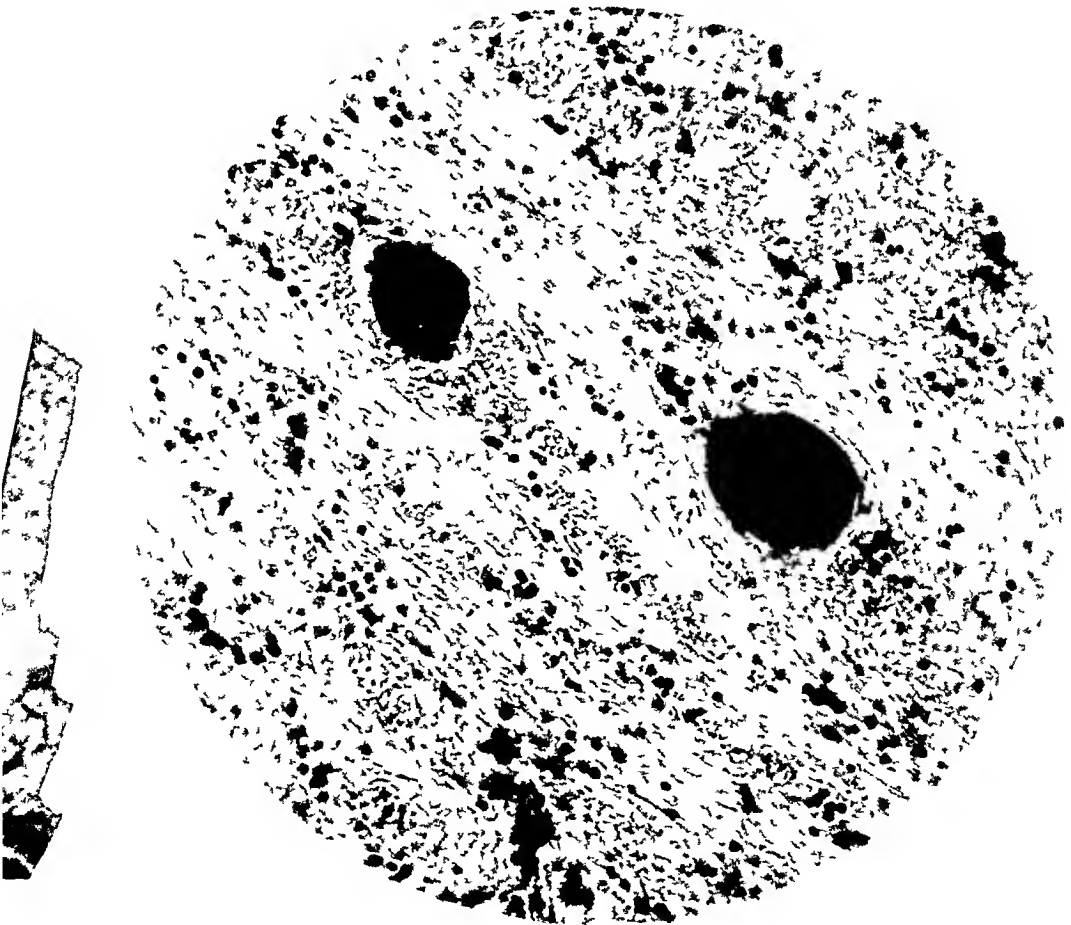


FIG 5 Microscopic section of the same brain as in figure 4 through the area with minute hemorrhages It shows two of such and extensive erythro-diapedesis elsewhere

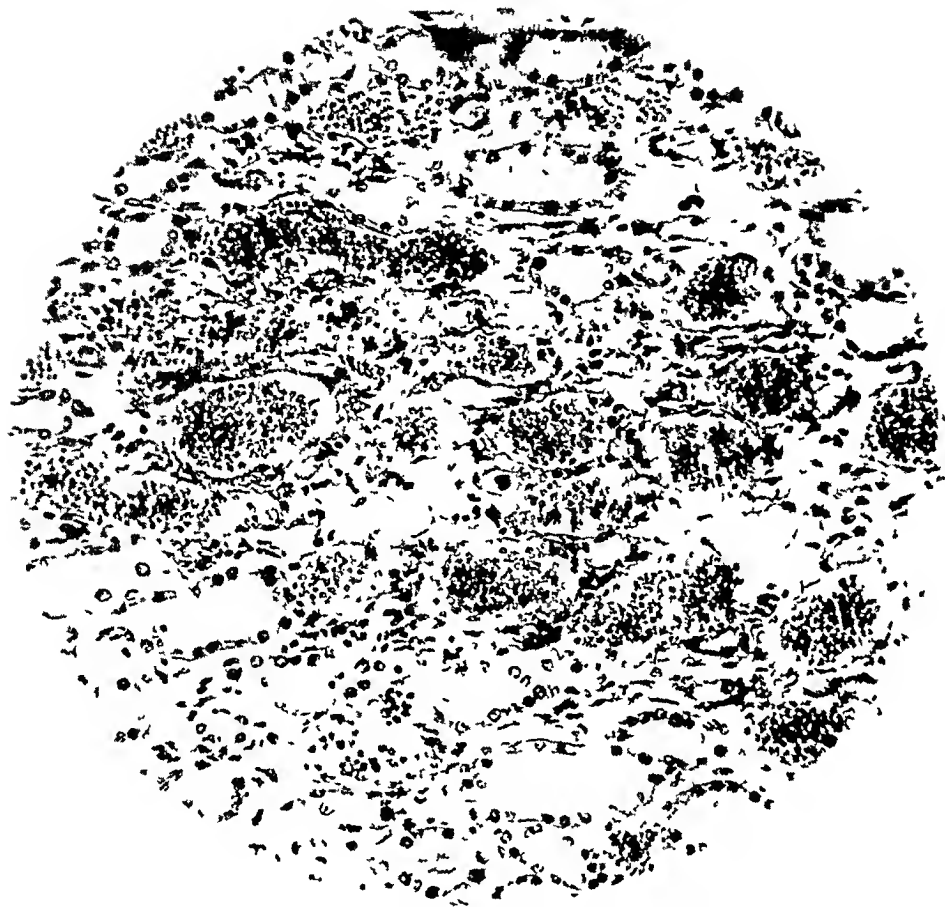


FIG 6 Microscopic section of the kidney in a case of eclampsia (same as in figure 4) It shows dilatation and engorgement of the arterioles with extensive erythro-diapedesis into the surrounding parenchyma

The use of the term "hemorrhage" when hypertension is present is not as expressive as "infarct" in the true sense of the word, as it is derived from the Latin "infarcire" meaning to stuff. The hemorrhagic extravasations in those conditions with associated hypertension seem undoubtedly to be due to vasoconstriction leading to slowing of the blood stream or peristasis, and then more or less extensive diapedesis of the erythrocytes into the surrounding tissues.

I wish to express my thanks to Dr W H Chase for permission to use the microscopic slide for figure 1, and for his generous help in the preparation of the pathological material.

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THE CLINICAL IMPLICATIONS OF THE THYMUS AND STATUS THYMICO-LYMPHATICUS^{*}

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OPINIONS concerning the clinical disturbances attributable to the thymus—to employ the metaphor of the pendulum—have swung from one end of the arc to the other, and the organ has been incriminated on the one hand as the cause of many symptoms, and on the other has been considered as relatively innocent and inoffensive. The truth of the matter probably lies somewhere between these two extremes, although it is not easy to know just where to arrest the pendulum. Confusion is increased by the fact that certain physicians, whose convictions must be received with respect, have expressed extreme views, sometimes doubting that the thymus ever causes manifestations which are clinically evident. Furthermore, much of the literature on this subject is cluttered with personal opinions and enthusiasm, unsubstantiated by facts, or, worse, based upon erroneous assumptions concerning the anatomic features of the thymus or unwarranted presumptions in regard to its functions and pathologic physiology.

Since this presentation is confined to the clinical aspect of the thymus in infancy and childhood much controversial matter may be eliminated.

One can approach the problem by propounding certain queries, the answers to which would be of great assistance to the clinician. Since the solution of these questions is not yet available, much discrimination must be employed in separating speculation from fact. It is this that we are attempting from the viewpoint of the physician who is frequently faced with the interpretation of symptoms and the indications for treatment.

What are the symptoms which could be caused by enlargement or disorders of the thymus gland? Put more specifically. Can enlargement of this structure cause dyspnea, crowing respiration, cough and cyanosis, and can disturbance in its function be a factor in convulsions and sudden death, or lead to such conditions as pylorospasm?

The anatomic relations of the thymus must be considered. In early life it occupies a position in the lower anterior portion of the neck and extends behind the upper part of the sternum. It is attached to and overlies the upper part of the pericardium and is in intimate contact with the left innominate vein, the superior and inferior vena cava, the pulmonary artery, and with the vagus, phrenic and recurrent laryngeal nerves. The size of the thymus at different ages has been a source of great confusion, largely because observations were on pathologic subjects. It has, however, been demonstrated,

^{*} Read at the Chicago meeting of the American College of Physicians April 20, 1934.
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particularly by Boyd,¹ that the weight and dimensions of the organ are dependent to a great extent upon the general nutritional state of the body, so that in a poorly nourished or dehydrated child it may be only one-half or one-third of the size it possesses in a well nourished child of the same age. With certain illnesses, its tissue may decidedly diminish, even though there is relatively little loss in general body weight. Of some importance is the fact that there is a decided temporary decrease in the weight of the thymus from birth to about two weeks of age. With this exception, however, it should be noted that, while it increases in weight until about the age of puberty, its size in relation to total body weight is decreasing.

Many authors have denied the possibility of even a greatly enlarged thymus, relatively soft organ that it is, causing compression of a stiff, cartilaginous trachea. It has been claimed, for example, that it requires a weight of about 1000 grams to close the trachea of an infant. Such observations are interesting, but there is no proof that an enlarged thymus during life might not exert such a pressure. It is held by some clinicians that any swelling of the thymus would follow the path of least resistance, and expansion would take place laterally rather than in the antero-posterior direction in which tracheal compression would be brought about. There is, nevertheless, no proof that there is less resistance in the neck or in the thorax to expansion in a lateral direction than in an antero-posterior one, and it is to be noted that the chief danger from compression of the trachea would be in the bony and rigid thoracic inlet, where there is relatively little chance for expansion in any direction.

Can the thymus actually compress the trachea, and what is the evidence for this? Necropsy studies of this problem can be criticized because distortion of antemortem conditions might take place, and edema and congestion of the thymus, which may have been the active factors, disappear after death. The most direct evidence would be visual demonstration during life. Jackson, quoted by Pancoast,² has claimed to have seen tracheal compression by the thymus by means of the bronchoscope in over 300 patients who had obstructive symptoms as wheezing, dyspnea, and impending asphyxia. Pancoast and others have apparently demonstrated roentgenologically that the thymus actually can cause compression of the trachea. Additional support that compression occurs might be adduced from the clinical observation that thymectomy and the reduction in size following radiologic treatment of the thymus cause cessation of obstructive symptoms. The fact that symptoms which could be attributed to thymic pressure appear largely in the first year of life is of interest in this connection, since, while increasing in size after that time, the thymus is not growing at the same rate as the chest, and, therefore, becomes relatively incapable of causing pressure.

As already noted, the trachea is not the only structure with which the thymus is in contact. For example, in the bony thoracic inlet the laryngeal nerves might be compressed by a turgid or hyperplastic thymus, and the unilateral or bilateral paresis or paralysis of the vocal cords, resulting

from this might be a cause of such symptoms as noisy breathing, stridor, brassy cough, or, it is claimed, in some instances of death. Pressure on other nerves is unlikely. On the possibility of pressure upon the great vessels with reduction of their lumen and resultant cyanosis, there may be cited the work of Noback,³ from which he concluded that an increase in the antero-posterior extent of the thymus could compress these structures, and that in some of the cases studied at necropsy this had evidently occurred. The esophagus may apparently also be compressed, and this would account for the difficulty in swallowing already mentioned. Cyanosis of the head, neck and upper extremities has been described as a rare accompaniment of enlarged thymus. It could be explained by pressure on the left innominate vein, and that this can actually occur is indicated by one of Noback's dissections.

Much that is stated concerning the functions and physiology of the thymus is the result of speculation and rests upon hypothesis only. The methods of study have varied widely and include observation of histologic structure, of the supposed results of enlargement, of the effects of extirpation and of experiments with feeding or injecting extracts of the gland. Even if time permitted it would be presumptuous on my part to analyze critically these studies, when the most careful and earnest observers often disagree both in results and interpretation. It is easy to point out, however, that histologic structure is difficult to correlate with function, that extirpation of the thymus in animals, or the feeding, injection or implantation of it, does not necessarily indicate that a similar effect would be observed in man, that any after-effect from excessive radiation of the thymus has not been convincingly demonstrated, that, while there may be synergy of the thymus with certain organs of internal secretion, particularly the adrenals, further study is required to conclusively demonstrate this fact. None of this is to say that the thymus is functionless or physiologically inactive, but rather that there is so much uncertainty with regard to this structure that the physician is forced to solve his clinical problems without the assistance that more accurate knowledge would give him.

In the attempt to evaluate the significance of some of these symptoms in their relation to enlarged thymus we have studied a group of 197 infants and children in whom roentgenologic examination had been made, of these, 116 had thymic shadows greater than normal, and 81 did not. The latter group was secured largely by routine roentgenograms of the thymus taken on cleft palate and hare-lip cases. The value of roentgenograms in the diagnosis of enlargement of the thymus will be discussed later.

By means of the four-fold table an analysis was made of the entire group of 197 patients, when they were divided into four mutually exclusive groups as follows

- (a) 80 with enlarged thymus and symptoms (convulsions, dyspnea, including suffocative attacks, crowing respiration, cough, cyanosis, pylorospasm, sudden death),

- (b) 36 with enlarged thymus but without the foregoing symptoms,
- (c) 43 with no enlargement of the thymus but having the foregoing symptoms,
- (d) 38 with no enlargement of the thymus and without the foregoing symptoms

The object was to ascertain whether the symptoms were significantly associated with an enlarged thymus gland. The χ^2 was 2.26. The mathematical implication is that all four groups came from the same universe, i.e., that the symptoms considered are not inevitably associated with enlarged thymus. Such would be the conclusion from a clinical point of view, but it is interesting that this can be supported by mathematical analysis.

If, however, these 197 patients are divided into two groups according to the presence or absence of enlarged thymus (see table 1), it is seen that

TABLE I
197 Infants and Children

| | No Symptoms | Con- vul- sions | Dysp- nea | Cya- nosis | Crow- ing Resp | Cough | Pyloro- spasm | Sudden Death | Total Symptoms |
|-------------------------|----------------|-----------------------|--------------|---------------|----------------------|-------|------------------|-----------------|-------------------|
| Thymus Enlarged, 116 | 36 | 21 | 22 | 33 | 10 | 21 | 20 | 7 | 80 |
| Thymus Not Enlarged, 81 | 38 | 2 | 10 | 12 | 0 | 7 | 33 | 1 | 43 |

of the 116 children with enlarged thymus gland, 80 (69 per cent) had symptoms. Contrasted with this group is another of 81 children who did not have enlarged thymus glands, yet 43 (53 per cent) of these had symptoms similar to the former group. When these groups are analyzed according to the Chi-square test, χ^2 is 6.39, showing that these two groups are not from the same universe. Further analysis of the rate of incidence of the various symptoms shows that most of these are more apt to be associated with enlarged thymus than with one of normal size according to the roentgenogram.

It should be stated that in the 80 patients with enlarged thymus glands and symptoms, there were complicating conditions in 56 (70 per cent) which might have been responsible for these symptoms. In an attempt to evaluate these factors a further Chi-square test was done, using as the universe only those 80 patients who had an enlarged thymus, and subdividing this universe into two groups (table 2) as follows:

- (a) 24 patients who had symptoms but in whom it was impossible to attribute these to any other cause than enlarged thymus, and
- (b) 56 patients* who had symptoms which might equally well have been at-

* These 56 patients, in addition to enlarged thymus had other conditions as follows: Infections of the upper or lower respiratory tract in 20 instances, increased intracranial pressure in 11, congenital heart disease in 6, pylorospasm in 6 (included in this group since there were no other symptoms than pylorospasm), spasmophilia in 3, pulmonary atelectasis

TABLE II
80 Patients with Enlarged Thymus

| | Con- vul- sions | Dysp- nea | Cya- nosis | Crow- ing Resp | Cough | Pyloro- spasm | Sudden Death |
|---|-----------------------|--------------|---------------|----------------------|-------|------------------|-----------------|
| Symptoms Due to Enlarged Thymus, 24 | 5 | 6 | 10 | 4 | 5 | 12 | 3 |
| Symptoms Possibly Due to Some Other Cause, 56 | 16 | 28 | 22 | 6 | 17 | 4 | 4 |

tributable to some other cause or disease condition present in the patient at the time

It was shown that these two groups also came from different universes, the sigma ⁴ being 4.47. The rate of incidence of symptoms was higher in those patients with an enlarged thymus gland who had other reasons for these symptoms, the exceptions being only sudden death and pylorospasm. (The latter could be explained by the fact that all cases of pylorospasm were included in the "pure" thymus group unless shown by operation to be true pyloric stenosis.) The implication here is that a child with an enlarged thymus gland and some complicating factor, as respiratory infection, is more liable to have symptoms than a child with an enlarged thymus gland only, and this would be logical from a clinical viewpoint. It should be stated, however, that the mathematical analysis was complicated by the fact that the symptoms were not mutually exclusive, and it is obvious that all of the symptoms are such that an enlarged thymus is not necessary in their production.

The interesting association of enlarged thymus with pylorospasm has been described by a number of authors, who have brought forward as explanation the theory that the pylorospasm and the enlarged thymus are both dependent upon vagotonia, the result of insufficient adrenalin production. Of our 116 patients who had an enlarged thymus 20 had symptoms of pylorospasm, and of our 81 patients who did not have an enlarged thymus 33 had symptoms of pylorospasm (see table 1). When the rate of incidence is considered it is seen that, since the rate is more than twice as great (33/81) in the negative thymus group as in the positive thymus group (20/116) there is obviously no significant association between pylorospasm and enlarged thymus.

Is there such a condition as status thymico-lymphaticus or lymphatism?

The chief manifestation attributed to this diathesis is sudden death occurring without obvious cause, during anesthesia, or following such supposed factors as hypodermic injection, the administration of diphtheria antitoxin or of nonprotein material or drugs, chilling, extraction of teeth, fracture of the jaw, acrodynia in 2, enlarged bronchial glands in 2, esophageal atresia in 1, snuffles from syphilis in 1, muscarin poisoning in 1, asthma in 1. The various symptoms analyzed, such as convulsions, dyspnea, cyanosis and the like, present in these children could, as stated, equally well have been attributable to such conditions rather than to an enlarged thymus.

tures, psychic shock and the like. In the conception of status thymico-lymphaticus it is not necessary to believe that death or other symptoms are due to pressure of an enlarged thymus—in fact, some of the most ardent advocates of the existence of “lymphatism” find it difficult to assume this explanation. When the thymus is enlarged this is considered only a secondary phenomenon. In many studies there has been discovered no constant enlargement of the thymus in sudden death from unexplained causes.

In our present series of cases there were eight instances in which sudden death had been thought to be due to status thymico-lymphaticus. By roentgenograms or necropsy the thymus was found to be enlarged in seven. In three cases, two of which were studied by necropsy and enlarged lymphatic structures discovered, there was no factor found to account for death other than a possible status thymico-lymphaticus. Of the remaining five, necropsy showed in two congenital heart lesions, in one there was esophageal atresia, in one there was found at necropsy a cystic type of degeneration of the internal capsule, and in one, death had probably been due to muscarin poisoning.

It would appear to be fair to state that sudden death occurs in some cases in which it cannot be attributed to any well defined cause, but in which there is found hypertrophy of the lymphoid structures throughout the body, and at times a hypertrophied thymus gland. Further study may perhaps show that this is associated with disturbed function of the thymus, or more likely that the so-called thymico-lymphaticus is a secondary or related manifestation of some other alteration of body equilibrium.

Many of the explanations given for sudden death in status thymico-lymphaticus, as the effect of an unknown toxin, “hyperthymization,” “lymphotoxemia,” vagotonia, deficiency of the chromaffin system, and allergic reaction, are resounding in terminology but have little or nothing to uphold them. The theory of adrenal deficiency, however, has much in its favor, and is supported by certain physiologic and pharmacologic facts, a discussion of which lies outside the province of this presentation. Adrenal insufficiency seems to be a possible explanation of certain cases of sudden death which can be accounted for in no other way. What this has to do with the thymus is another matter, although there may be an associated thymic and lymphoid hyperplasia, and it is interesting that in adrenalectomized animals there follows hypertrophy of the thymus. That cerebral hemorrhage is sometimes a cause of sudden death in children with enlarged thymus glands and lymphoid hypertrophy is undoubtedly true, and we have seen at least two such cases in which histologically there appeared to be thin-walled blood vessels and also small hearts. Cerebral hemorrhage, however, could account for only a relatively few instances of sudden death. Infrequent, too, is “thymic apoplexy” in which there is extensive hemorrhage into the thymus gland. This condition is, at any rate, probably associated with syphilis, and if so, does not belong in the category of ordinary thymic hyperplasia or status thymico-lymphaticus.

How is the clinician to diagnose thymic enlargement and status thymico-lymphaticus?

It does not appear correct to discard entirely the possibility of the effect of pressure by the thymus. It should be one of the causes to be investigated in dyspnea, stridor, crowing respiration and cyanosis, and perhaps also in other symptoms such as brassy cough, suffocative attacks and the like. Percussion is of little value in outlining the lateral dimensions of the thymus, and the interpretation of it difficult unless the organ be greatly enlarged. Even if an increased area of dullness is found over the manubrium, this by no means eliminates the possibility that other intrathoracic structures may be responsible for it. Furthermore, it is quite likely that increase in the antero-posterior diameter of the thymus—a situation impossible to elicit by percussion—may be more important than lateral expansion of it. Increase of obstructive symptoms produced by flexion of the head, a procedure emphasized by some, does not differentiate thymic pressure from other causes of obstruction.

In regard to the diagnosis of status thymico-lymphaticus, little more can be stated than has already been mentioned. It would be difficult indeed to detail the diagnostic aids for a condition the pathogenesis of which is so little understood, and the very existence of which is denied by many. More and more reports indicate that careful postmortem examination would eliminate from the category of "thymus deaths" many cases formerly so classified. The weight of recent evidence, too, as already stated, whether obtained by anatomic or roentgenologic study, is against any correlation between undue oversize of the thymus and sudden death.

The merits of the demonstration of thymic enlargement on the roentgenogram must depend upon a correct evaluation of the size, shape and position of the organ in normal infants, and in addition the effect produced by respiration and the position of the patient. Most clinicians would agree that roentgenograms taken casually and only during one phase of respiration furnish little information concerning the size of the thymus. More work is needed to establish average boundaries, and this is rendered difficult by the fact that the normal size of the organ at any age in infancy or childhood is decidedly variable, and also that there are racial and geographic differences. That is to say, it cannot be stated that a shadow greater than a certain width is necessarily indicative of thymus enlargement, nor that it proves that obstructive symptoms are due to this. In fact, the roentgenogram may not infrequently disclose a greatly enlarged thymus when no symptoms are present. Probably something can be learned from lateral views concerning compression of the trachea. Perhaps it is fair to state that clinical symptoms are of as much, if not more value in the diagnosis of thymic pressure than are roentgenograms, unless the latter are taken and interpreted by experts with experience.

A few authors have claimed to have found considerable value in the fluoroscope in the visualization of the thymus and its compression of the trachea.

It would probably be a safe procedure to consider the possibility of thymic pressure in all cases of asphyxia, stridor, wheezing, brassy cough and cyanosis in infants, but to realize that it is a relatively infrequent cause of these symptoms. After the period of infancy, tracheal obstruction is still less apt to be caused by the thymus. It is always well to remember, too, that a moderate enlargement of the thymus might be a factor in adding to pressure produced by some other means. For example, an infant with an upper and lower respiratory infection might be further embarrassed in respiratory effort by an enlarged thymus which previously or subsequently would exert no effect. On the contrary, a presumably enlarged thymic shadow in an infant with obstructive symptoms should not be accepted as diagnostic and entirely explanatory of the symptoms, search must always be made for other possible causes of pressure.

We would like to emphasize the necessity for search for intrinsic and extrinsic sources of tracheal compression by palpation or inspection of the throat or by the use of the laryngoscope, bronchoscope or roentgenogram. The type of stridor is usually of little diagnostic value, and it has been our experience to see mistaken for thymic obstruction such conditions as foreign bodies, pulmonary atelectasis, lingual tumors, retropharyngeal abscess, stenosis of the larynx, abductor paralysis, papilloma of the larynx, and diphtheritic and other forms of laryngitis and tracheitis. Asthma, which may occur even in infancy, has been confused with thymic asthma. The danger of incorrect diagnoses in the conditions mentioned is obvious, since many of them are curable if recognized early, but may proceed to the necropsy table if the symptoms have too long been attributed to the thymus.

Convulsions not explicable on an organic or toxic basis should, in early life, lead to a suspicion of spasmodophilia rather than to a diagnosis of thymic disturbance.

Paralysis of the recurrent laryngeal nerve might in rare instances be due to thymic pressure. Cyanosis may be an accompaniment of many of the previously mentioned causes of respiratory symptoms, but in early life it is more frequently caused by congenital heart disease and pulmonary atelectasis or other pulmonary lesions than by laryngeal obstruction.

SUMMARY

Mathematical study has been carried out on a group of 116 infants and children who, according to roentgenograms, had an enlarged thymus, using as a control group 81 infants and children who did not have an enlarged thymus by the same criterion. Clinical impressions previously held were strengthened by the analysis. It would appear that certain statements can be made with reasonable assurance.

- 1 In some instances an enlarged thymus gland can cause pressure upon structures in the thoracic inlet and lead to the development of such symptoms as dyspnea, suffocative attacks, crowing respiration, cough and cyanosis.

- 2 The symptoms mentioned occur with many other diseases and ab-

normal conditions and these are perhaps more frequent causes of all of them than is enlarged thymus

3 An infant or child who has some cause for dyspnea, cough and cyanosis, as respiratory tract infection, congenital heart disease and the like, and who also has an enlarged thymus is more liable to develop these symptoms. Probably an enlarged thymus may aid in their production, even in such instances where in itself it would be insufficient to cause symptoms

4 From a mathematical point of view there is no significant association between enlarged thymus and pylorospasm

5 There is no proof that convulsions are associated with enlarged thymus, and their presence even in a patient with an enlarged thymus gland should lead to a suspicion that increased intracranial pressure, spasmophilia (tetany) or some other cause exists

6 An enlarged thymus according to roentgenograms is by no means necessarily associated with symptoms

7 Even when obstructive symptoms are present in an infant or child with an enlarged thymus, search must be made for other possible causes

8 This study furnishes no solution to the question of the relation of sudden death, not explicable by some discoverable cause, to status thymico-lymphaticus

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THE CLINICAL MANIFESTATIONS OF AMYLOIDOSIS*

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THE recent widespread use of the Congo Red test for the clinical determination of amyloidosis has aroused much interest in a subject which for the past two or three decades had been looked upon more as a pathological curiosity than as a clinical entity. The favorable results originally submitted by Bennhold¹ 10 years ago have been repeatedly confirmed by other observers. Bookman and Rosenthal,² Schonberger and Rosenblatt,³ Nemeth,⁴ Shapiro,⁵ Wallace,⁶ and many others have reported corroborative evidence of the diagnostic value of the test. The observation by Bennhold, and others, that in certain nephrotic states there was an escape of the dye by way of the urine thus giving false readings was originally thought to be an important limitation, but subsequent quantitative studies have shown that the amount of the dye eliminated this way is too small to appreciably alter the determinations. Barker and Snell⁷ found that the largest amount of dye which had escaped by way of the urine in the course of any experiment did not exceed 2 per cent. In general, all who have worked extensively with the Congo Red test have found it an accurate procedure for ascertaining the presence of amyloidosis and agree with Rudolph⁸ that the examination produces no ill effects and that the percentage of error is very small. With minor variations, the criteria for interpretation established by Bennhold are still generally accepted. A positive diagnosis of amyloidosis should not be made unless over 50 per cent of the dye has been retained by the tissues in one hour. Because of this ability to make a definite premortem diagnosis there has been established a greater appreciation of amyloid disease as a clinical syndrome.

At the present time, even in large general hospitals, amyloidosis is encountered only on rare occasions. In a recent report from the Massachusetts General Hospital, Mallory⁹ stated that he had seen but four cases in six years. With the exception of tuberculosis institutions, similar conditions prevail everywhere. This low incidence, as compared with its common occurrence during the past century, has been attributed to surgical progress in the eradication of suppurative foci. It is difficult to state exactly how prevalent amyloidosis was during the nineteenth century but even before Virchow gave this form of degeneration its present erroneous name, lardaceous disease was a well known entity among English physicians. Probably the first description of amyloid disease in the literature was that of Hodgkin's¹⁰ in 1832, and many of the cases reported by Bright were really of lardaceous origin.¹¹ In 1854, Sanders¹² stated that waxy degeneration of

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the spleen, liver, and kidneys occurred in 10 per cent of all the necropsies at the Edinburgh Royal Infirmary Dickinson¹³ encountered 201 cases among the autopsies at the St George's Hospital between the years 1867 and 1894 but did not state what percentage of the total number the amyloid cases constituted Fagge¹⁴ found 244 instances at Guy's Hospital over a 21 year period From various other sources the impression is obtained that amyloidosis was a fairly common occurrence during the past century but it was stated by Leube¹⁵ that its incidence varied greatly in different localities even though the predisposing diseases might be equally prevalent

As was mentioned previously, very few clinicians have had the opportunity of studying large series of cases during the past 20 or 30 years Saleeby,¹⁶ in a series of 3047 consecutive necropsies at the Philadelphia General Hospital, found 50 instances of renal amyloidosis (17 per cent) which was approximately the total number of all the amyloid cases Waldenstrom¹⁷ observed 28 cases in 12 years Rosenblatt,¹⁸ in a series of 1727 consecutive necropsies at the Montefiore Hospital, found the incidence of amyloidosis to be 72 per cent Further analysis of these statistics reveals that tuberculosis has been by far the greatest etiologic factor in the production of amyloid degeneration and that, at the present time, it is the only factor of any significance In 504 cases at Guy's Hospital, cited by Herringham,¹⁹ it was the underlying disease in 37 per cent, in 430 cases at Edinburgh, collected by Gibson,²⁰ it was the etiologic agent in 45 per cent, and in Dickinson's series in 48 per cent Coming down to the present time its incidence is found still higher Saleeby found it the causative agent in 82 per cent, Waldenstrom in 93 per cent, and Rosenblatt in 88 per cent It is interesting to note that in the latter's report the incidence of amyloidosis among the tuberculosis patients was 244 per cent as contrasted with 12 among the patients with other types of chronic disease In the tuberculosis cases with suppurative complications such as pyothorax, or draining sinuses, the incidence was 352 per cent Fishberg,²¹ in his series, found that 44 per cent of the tuberculosis patients with suppuration had amyloid changes

It has been generally accepted by all writers on the subject that suppuration is the basic requirement for the development of amyloidosis It has also been stated that the only reason that tuberculosis, or any other systemic disease, can cause amyloid degeneration is through the intermediary of pus formation This contention has been well corroborated by statistical studies but it should also be realized that the absence of suppuration does not preclude a diagnosis of amyloidosis There was no evidence of pus formation in 17 per cent of Dickinson's cases and none in 60 per cent of the non-tuberculous and 29 per cent of the tuberculous cases in Rosenblatt's series Many other cases of amyloidosis without suppuration were reported by Bannick,²² Cabot,²³ Bannick and Barker,²⁴ Christian,²⁵ and others In addition to tuberculosis and local suppurative lesions amyloidosis has been found associated with almost every type of disease process including syphilis, leukemia, arthritis, multiple myelomata, cancer, bronchiectasis, pneumoconiosis,

osis, Hodgkin's, lymphosarcoma, and rheumatic heart disease. The high degree of tuberculosis incidence is in all probability due to the fact that it is one of the few diseases in which extensive tissue destruction and chronicity are combined, rather than to any peculiar relationship between the tubercle bacillus and amyloid. Syphilis which was formerly considered a very important cause of amyloidosis—most authors placed it next in frequency to tuberculosis—is now a very small factor. Bell²⁶ found it to be the underlying disease in four out of 65 instances, Rosenblatt in one out of 125, and Saleeby in none. This change has probably been brought about by the introduction of the Wassermann test and arsphenamine therapy. There have been recorded many instances in which even after necropsy there was disclosed no basic process to account for the development of the amyloid. These cases have been designated as idiopathic, or primary, amyloidosis and were described as early as 1856 by Wilks.²⁷

Inasmuch as the major etiologic agent in amyloidosis is a disease of young adults, amyloidosis occurs mainly in this age group. Most cases are found between the ages of 20 and 40 years but the disease has been reported in children as young as four years and in adults as old as 68. Sex is apparently no factor. It is practically impossible to determine accurately the time required for the development of amyloidosis because of the paucity of early manifestations. Waldenstrom¹⁷ observed that the onset of clinical amyloidosis usually occurred within one to two years after the appearance of the suppurative lesion. In Whitbeck's²⁸ series of bone tuberculosis cases the duration in each instance was at least two years. In Walker's²⁹ case of empyema, definite signs of amyloidosis occurred two years after the onset. At the Montefiore Hospital many cases of pulmonary tuberculosis were observed in which the clinical duration of the disease did not exceed two years and in which extensive amyloid disease was present on postmortem examination. It is unusual for amyloidosis to occur when the basic process is of less than one year's duration but exceptions have been noted. Dixon³⁰ reported eight cases with clinical history of less than one year, and eight of less than six months. Fagge³¹ discovered one instance of three months' duration following fracture of the spine, and Dickinson³² one of three weeks' duration following compound fracture of the lower extremity.

Amyloid degeneration has been found in almost every organ of the body—heart, lungs, trachea, liver, larynx, spleen, skin, tongue, adrenal, thyroid, kidney, pancreas, intestine, lymph node, parathyroid, diaphragm, seminal vesicles, conjunctiva, bladder, and even brain. However, most of these organs are seldom involved and some of them only in isolated instances. The clinical syndrome of generalized amyloidosis is produced by involvement of the liver, kidney, and spleen. There is some variation among different reports as to which of these organs is most frequently affected but there is general agreement that all three are simultaneously involved in at least 60 per cent of the instances. The spleen is often involved alone, the kidneys seldom, and the liver rarely. Next in importance to these

organs is the adrenal which is usually implicated in association with the other three. The clinical course of amyloid disease depends on the extent of degeneration of these organs. The one exception to this is the heart, extensive involvement of which produces myocardial insufficiency and a clinical picture which is entirely one of cardiac decompensation. The amyloid in these instances is usually confined to this organ. Such cases are exceedingly uncommon and are obviously most difficult to diagnose during life. A few instances have been recorded by Wild,³³ Steinhaus,³⁴ Beneke and Bonning,³⁵ Kann,³⁶ Lubarsch,³⁷ Larsen,³⁸ and Warren.³⁹

The constitutional symptoms associated with amyloidosis such as pallor, anemia, weakness, and cachexia are so interwoven with the underlying disease that it is inadvisable to consider them of diagnostic value. While it is true that many cases do have a typical waxy facies this is by no means a universal finding and its absence is of no importance. The distinguishing symptoms and signs of amyloid disease are the clinical manifestations of the degenerative process as it affects each particular organ. The extent of the physiologic changes produced by amyloid varies greatly among the different organs so that the clinical features of each case depend on the organs involved and the degree of involvement. This explains why so many instances are discovered only after postmortem examination. In Dickinson's⁴⁰ series 27 per cent of the cases presented no symptoms or signs.

Of the organs of major importance in amyloidosis the spleen is implicated the greatest number of times. In a study of 5000 consecutive necropsies Krumbhaar⁴¹ found 156 instances of splenic amyloidosis as compared with 83 of hepatic and 78 of renal involvement. Parkes⁴² found the spleen implicated in every instance of amyloid disease. Despite this high incidence, splenic amyloidosis produces practically no symptoms other than the sensation of having an enlarged organ in the abdomen, and extreme enlargements are unusual. Inasmuch as most of the patients are bedridden because of the underlying disease, the disturbances noted in other splenomegalies such as dragging feeling and pressure on the surrounding organs are usually absent. The amyloid spleen when palpable is felt as a hard and non-tender mass. Splenic amyloidosis produces no manifestations of splenic insufficiency and there has been no evidence reported that it in any way alters either the clinical course or the prognosis. Amyloidosis of the spleen presents no distinguishing features of diagnostic value.

Because of its size the liver shows the greatest amount of amyloid change and it is implicated in about 60 per cent of the cases. The large quantity of amyloid substance found in the liver on necropsy as compared with that in the other organs has given rise to the suggestion that it is the amyloid of the liver which produces retention of the Congo Red during performance of the test. Bookman and Rosenthal² state that a positive test is not obtained unless the liver is involved. This observation has been found generally correct but exceptions have been noted.¹⁸ The liver, like the spleen, also produces few symptoms. It is usually found enlarged and occasionally

extends into the pelvis. On palpation it is firm, smooth, and not tender. There have been few studies on the effect of amyloidosis on hepatic function. Such observations as have been recorded indicate that even the most extensive amyloidosis produces no impairment. According to Parkes⁴² icterus is never caused by amyloid of the liver and in those rare instances in which both icterus and hepatic amyloidosis co-exist it is not difficult to ascribe another cause for the jaundice. Dickinson⁴⁰ found one instance of jaundice among 65 amyloid livers and in this case there was also present an hydatid abscess. The writer has studied over a hundred cases of amyloidosis of the liver without encountering a single instance of jaundice. In two cases in which the bromsulphthalein test had been performed, Bannick²² found negative results. With regard to both liver and spleen there is a marked disproportion between the degree of involvement and the symptoms produced.

Most patients with generalized amyloidosis show signs of asthenia, hypotension, and failure of the peripheral circulation. Although adrenal amyloidosis has been found to occur in as much as 40 per cent of the cases¹⁸ these symptoms are to be interpreted as part of the syndrome of the basic disease rather than as due to adrenal failure. Inasmuch as Addison's disease is itself very uncommon it naturally follows that adrenal insufficiency due to amyloidosis must be exceedingly rare. However, a few authentic cases have been reported. In a series of 2550 necropsies, Philpott⁴³ found 14 cases of Addison's disease one of which was due to amyloidosis. Hunter and Rush⁴⁴ reported a case in a young adult with pulmonary tuberculosis and generalized amyloidosis. McCutcheon⁴⁵ described an instance in a patient with hypernephroma, and other individual cases were reported by Bitorf,⁴⁶ Schultz⁴⁷ and Schlesinger.¹⁸ It is to be emphasized that these citations represent the approximate total number of cases in the literature and that, in the usual course of events, amyloidosis of the adrenals produces no characteristic clinical features. Adrenal insufficiency due to amyloidosis was not observed in any of the large series of cases reported.

Ever since amyloidosis has been studied clinically it has been realized that the significant features are those produced by involvement of the kidneys. Of 86 cases which presented signs in Dickinson's⁴⁰ series, 76 were renal in origin. The most common sign of renal amyloidosis is albuminuria, particularly progressive albuminuria. This was noted in 90 per cent of Dickinson's cases, in 72 per cent of Saleeby's¹⁶ cases, and in 92 per cent of Dixon's³⁰ cases. In a patient suspected of amyloidosis, albuminuria which cannot be ascribed to any other cause is an important diagnostic consideration. However, the absence of albuminuria does not rule out renal involvement and many such instances have been reported. Waldenstrom¹⁷ states that even extensive amyloidosis may be present without albuminuria but, as has been pointed out by Leube,⁴⁹ these cases are to be considered as exceptions. The amount of albumin present in the urine is usually considerable, but the actual quantity varies greatly among patients. Most cases do not

exceed 10 grams daily even when the amyloid is very extensive, but Bartels⁵⁰ observed one with 32 grams. The average ranges between 2 and 5 grams. Bartels noted the presence of large amounts of globulin in the urine and thought that this finding might be of diagnostic import. Joachim⁵¹ described a low albumin-globulin ratio in the urine as did also Hiller⁵² who stressed this point as a differential between amyloid and other types of nephrosis. Although polyuria has been mentioned as a significant finding by Floyd,⁵³ Todd and Sanford,⁵⁴ and others it is a very variable occurrence and is probably associated more with disturbed renal function terminally than with any peculiarities of amyloid degeneration. Urinary casts are a common finding in the patient with renal amyloidosis. Saleeby found them present in over 90 per cent and Dixon in 79 per cent of the instances. Hyalin casts predominate, but granular, epithelial, and waxy casts are also present. Amyloid casts have been mentioned by many authors but there is no evidence which warrants an expenditure of time searching for them. Dickinson⁵⁵ found them rarely, Leube⁵⁶ and Stewart,⁵⁷ never, and Saleeby discovered one questionable instance in a detailed study of the kidneys of 50 cases. White and red blood cells occasionally appear in the urine but their absence or presence is of no particular significance. Bannick and Barker²⁴ reported one case with definite hematuria.

Edema has been found a common occurrence in amyloidosis of the kidneys but its incidence has varied greatly among different observers. Parkes⁴² noted it in 82 per cent of the instances, Dickinson⁵⁸ in 75 per cent, and Bell²⁶ in 50 per cent. On the other hand, Todd⁵⁹ found it only in a small number of instances, Stewart⁶⁰ in 6 per cent and Dixon³⁰ and Rosenblatt¹⁸ in 24 and 34 per cents, respectively. This marked discrepancy is undoubtedly due to the fact that there have been included many instances in which the edema, although coexistent with the renal disease, had been caused by some other condition. The presence of edema in patients with minimal as well as maximal deposits of amyloid in the kidneys led Bell to conclude that there was no causal relationship between the two conditions, but recent studies on nephrosis have suggested a very definite connection. As the amyloid process progresses in the kidneys there is associated a definite increase in the quantity of albumin in the urine. At the Montefiore Hospital many cases were followed in which the clinical extent of the amyloidosis, as measured by retention of the Congo Red, increased simultaneously with the amount of albuminuria. On necropsy the widespread replacement of glomerular tissue by amyloid gave evidence that the kidneys had shared in the progressive increase of amyloid degeneration. The urinary protein is derived from the blood serum protein and as a result of the increasing proteinuria there occurs a progressive depletion of the total serum protein, particularly serum albumin. Because of this diminution in the serum protein there results a marked lowering of the colloid osmotic pressure of the blood.⁶¹ When the serum proteins have been reduced sufficiently the osmotic pressure is no longer able to counteract the hydrostatic pressure in the

capillaries and edema is produced in the same manner that was described by Epstein⁶² for chronic lipoid nephrosis. Examination of the subcutaneous edema fluid found in renal amyloidosis⁶³ discloses that it is poor in protein and similar to that in lipoid nephrosis. The attempts of Shapiro⁵ and others to postulate the existence of an associated lipoid nephrosis in order to explain the nephrotic syndrome in renal amyloidosis have not been convincing. Both clinical and pathological evidence favors the impression that glomerular destruction by amyloid produces the albuminuria and that the clinical features are a consequence of the loss of serum protein. It has been noticed by Floyd,⁶³ Fishberg,⁶⁴ and others that while the blood and urinary findings in amyloid and lipoid nephrosis are very similar with respect to albuminuria, low total serum protein, and inversion of the serum albumin-globulin ratio, the lipemia in the former is much less pronounced. Elevated cholesterol values have been found to occur in about half the instances and doubly refractile bodies are found in the urine only rarely. The cachectic state of the amyloid patient has been suggested as an explanation for the failure of lipemia to occur consistently.⁶⁴ The edema produced by renal amyloidosis is usually moderate and is confined, chiefly, to the lower extremities. Ascites is infrequent.

The absence of hypertension is one of the most distinguishing characteristics of renal amyloidosis. Even when the degenerative process has been so extensive as to cause nitrogen retention, elevation of the blood pressure is rarely seen.^{22, 65} Whether this is due to the debilitated condition of the patient or to some special features of the amyloid, itself, is not known. Of 79 instances of renal amyloidosis in Rosenblatt's series¹⁸ there was found no blood pressure which exceeded 140 mm systolic and only four which exceeded 130 mm. There have been reported, however, a few isolated cases in which uremia due to amyloidosis was accompanied by hypertension. Cardiac hypertrophy and retinal changes have likewise been encountered on rare occasions. Dickinson⁶⁶ observed a case with retinal hemorrhage and cardiac hypertrophy and mentioned a similar one seen by Allbutt. Fishberg and Oppenheimer⁶⁷ described a case with hypertensive neuroretinitis. Noble and Major⁶⁸ also reported an instance of this kind and there are several more occurrences mentioned in the literature. The percentage of uncomplicated cases of renal amyloidosis which terminate in uremia is small but it is to be emphasized that the condition is not a rarity. Dickinson⁶⁹ found it in 10 out of 95 cases (10.4 per cent) and Dixon³⁰ in seven out of 100 (7 per cent). At the Montefiore Hospital in a series of 87 cases, eight (9.2 per cent) were found to have died of renal insufficiency. According to Bartels⁷⁰ and Parkes⁴² early pathologists, including Rokitsky, regarded the amyloid kidney as a form of Bright's disease and even up to recently the uremic manifestations were attributed to a coexisting nephritis. However, the above figures as well as case reports by Zadek,⁷¹ Linder,⁷² and others clearly demonstrate that amyloidosis of the kidneys can produce renal insufficiency without a concomitant chronic nephritis or vascular disease. Fur-

thermore, it is not necessary that the renal disease progress until contraction occurs. The amyloid contracted kidney is an uncommon occurrence. In the eight cases with uremia at Montefiore it was found but once, and in Dixon's seven cases it never occurred.

It is to be seen, therefore, that although amyloidosis is a generalized disease consistently and extensively affecting the most important organs of the body, the course of the illness is essentially that of the underlying disease. There is no definite evidence that either amyloidosis of the spleen or of the liver was ever directly responsible for the death of a patient and there are only a few isolated reports that adrenal insufficiency was ever caused by amyloid involvement. The kidney, which presents the most striking clinical manifestation of amyloidosis, produces a fatal termination in but a small percentage of instances. The combined statistics of Dickinson, Dixon, and our own (305 cases) give the average incidence of uremia as 9 per cent and, as only about 75 per cent of the amyloid cases have renal involvement, the average incidence of terminal uremia in generalized amyloidosis is less than 7 per cent. In view of these findings one may make the general conclusion that in over 90 per cent of the instances amyloidosis, *per se*, is not the cause of death. When the nephrotic syndrome occurs in a case of renal amyloidosis it is indicative of extensive degeneration but many cases have been observed to continue in this condition for many years depending on the course of the etiologic disease. Christian²⁵ reported a case of idiopathic amyloidosis in which extensive edema and albuminuria were present for over three years, and Linder⁷² described a case of amyloid nephrosis secondary to chronic mastoid disease which had lasted for nine years. Stewart⁷³ and Wagner⁷⁴ reported instances of renal amyloidosis which had persisted for 10 and 15 years, respectively.

Both Bartels⁷⁵ and Dickinson⁷⁶ stressed diarrhea as an important symptom of amyloidosis and the latter stated that it was the cause of death in 8 per cent of the cases. He was puzzled, however, by the marked discrepancy between the small amount of amyloid found in the gastrointestinal tract on necropsy and the pronounced clinical symptoms. Observations among the amyloid cases at the Montefiore Hospital reveal the frequent occurrence of diarrhea. But, as the majority of the patients have tuberculosis, we have been inclined to consider the diarrhea as a symptom of the basic disease. There is statistical corroboration of this view in that 65 per cent of the tuberculosis patients have enteric tuberculosis⁷⁷ and only 6 per cent have enteric amyloidosis²¹. Inasmuch as so many of Dickinson's patients were also tuberculous, it is possible that the same situation existed.

When amyloidosis develops in the course of an illness it is indicative of a poor prognosis only because it reflects an unfavorable condition of the underlying disease. As has been indicated amyloidosis, in itself, modifies the clinical course in a very limited number of instances. Both animal experimentation and clinical observations have demonstrated that amyloidosis can undergo spontaneous resolution when the etiologic factor has been removed.

Kuczinski⁷⁸ showed this in studies with mice and clinical reports of cures were made by Fagge,⁷⁹ Gairdner,⁸⁰ Herringham,⁸¹ Walker,²⁹ and Waldenstrom¹⁷ The reason that spontaneous resolution is not more commonly observed is that the etiologic disease is usually one which progresses to a fatal termination In those instances in which the cause of the amyloidosis is a disease amenable to therapy, such as a local suppurative process, resolution will follow upon the healing of the primary disease

Many unsuccessful attempts have been made to introduce specific therapy for amyloid degeneration Potassium iodide, liquor potassium, and various other alkalis were the favorite drugs of the earlier writers Iodide therapy was probably beneficial in those instances in which the amyloid had been due to lues Whitbeck²⁸ recently introduced the use of concentrated liver and reported excellent results in five out of seven patients with osseous tuberculosis It is interesting to note, however, that in the five cases in which the amyloidosis had improved, there also had occurred an associated improvement of the primary bone disease and that in the two fatal cases death had not been due to amyloid involvement The parallel relationship between the course of the amyloid disease and that of the etiologic disease makes it rather difficult to attribute any specific therapeutic action to the liver feedings with respect to amyloid absorption

SUMMARY

The widespread use of the Congo Red test has transplanted amyloidosis from the realm of pathology to that of clinical medicine Unfortunately, this diagnostic aid has come to us at a time when amyloid disease is an unusual occurrence With the exception of tuberculosis, in which it has always been a prominent complication, amyloidosis at the present time is encountered in the average general hospital only on rare occasions Recent studies have revealed that amyloidosis may be associated with almost any type of disease, with or without suppuration, and that in many instances no etiologic agent is discovered even after postmortem examination As the major underlying disease, tuberculosis, is one of young adults, it naturally follows that amyloidosis is found mainly in this age group and, omitting exceptional instances, it takes from one to two years for the degeneration to manifest itself The ability to make a clinical diagnosis depends on an appreciation of the physiological and pathological changes produced by the degenerative process on the organs most frequently involved Constitutional characteristics such as anemia, cachexia, and waxy pallor are too intimately related with the underlying disease to be of diagnostic import When degeneration of the liver and spleen is sufficiently extensive these organs may be felt as hard, smooth, non-tender masses Involvement of the adrenals is a frequent occurrence and, although many amyloidosis patients exhibit features of adrenal insufficiency, true Addison's disease has been found on exceedingly rare occasions It is degeneration of the kidneys which produces the characteristic manifestations A patient with tuberculosis, or other debilitating disease, who shows progressive albuminuria,

depletion of serum protein, inversion of the serum albumin-globulin ratio, edema, no hypertension, and other associated findings of the nephrotic syndrome warrants a tentative diagnosis of amyloid nephrosis. The Congo Red test furnishes the confirmation. The number of proved cases of amyloid nephrosis overwhelmingly exceeds that of chronic lipid nephrosis and many instances have been recorded in which the latter diagnosis had to be changed to that of renal amyloidosis after postmortem examinations. It appears, therefore, that even in the absence of the diseases usually associated with amyloidosis any occurrence of the nephrotic symptom-complex requires the performance of the Congo Red test. There is a marked disproportion between the extent of amyloid degeneration and its effect on the clinical course of the patient. Despite the most widespread affection of the liver, spleen, and adrenals, in the great majority of instances, the ultimate prognosis will be entirely independent of the amyloid disease and depend only on the course of the underlying condition. In a small percentage of the cases renal amyloidosis terminates in uremia but extensive degeneration may be present for many years without any clinical manifestations of renal impairment. Many attempts have been made to introduce specific therapy for amyloidosis but their success has been found directly proportional to the behavior of the basic disease. Experimental and clinical observations have revealed that when the causative agent is removed the degeneration regresses spontaneously. However, as most of the cases are caused by diseases which terminate fatally, amyloid regression is an unusual occurrence.

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NON-PAINFUL FEATURES OF CORONARY OCCLUSION *

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THE symptoms signalling the onset of occlusion of a coronary artery with infarction, when thrombosis furnishes the determining factor in completing the closure, are striking and dramatic. In times past, certain reasons no doubt contributed to the failure of clinical recognition of the nature of the pathologic process causing the symptoms. Prominent among these reasons is a certain similarity in the character of the pain to that in the angina pectoris of effort and the fact that coronary occlusion often develops in patients with that symptom-complex, or less often may furnish a basis on which later anginal symptoms develop. The mere fact that the pain with thrombosis is more prolonged, does not cease with cessation of effort, and is accompanied and followed by signs of persisting damage in the myocardium, did not become recognized until recent years and is still too often disregarded by the family physician and surgeon. The early, frequent, routine study of the leukocyte response in the blood, and of the body temperature under conditions not clearly inflammatory or infective has been useful in establishing the presence of infarction, while the growing availability of electrocardiographic data has made the diagnosis common.

In the famous thesis by Rene Marie¹ in 1896 there is a clear statement of the pathologic relationship or sequence of coronary sclerosis, coronary thrombosis and infarction of the heart wall with resulting rupture of the heart, fibrous plaques in the myocardium, cardiac aneurysm and intraventricular thrombosis.

It is interesting in this connection to note the clarity with which Marie brings out the distinction in the histories of the cases between the angina of effort which he ascribes to a purely functional ischemia, and those other anginal paroxysms in which the ischemia becomes organic, due to a definite arterial obliteration and announced by a paroxysm in general more violent and more prolonged. The symptoms accompanying this *angor pectoris* and *mal angineux* are brought out with interesting detail and accuracy. Cases of infarction without pain are recognized. It is shown that survival is common, with development of fibrous plaques and of parietal aneurysm. He writes "Diagnosis is easy enough," and adds that it is not in the power of any therapy or medicament to restore life and function to this ischemic and necrotic part of the organ.

Although Dock² in 1896 reported a case of coronary thrombosis, recognized during life and proved at autopsy, and Huchard³ in 1899, and Krehl⁴ in 1901, discussed coronary thrombosis from the clinical standpoint, it re-

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maintained for Obratzow and Straschesko⁵ in 1910 to call attention to the feasibility of clinical diagnosis, and for James B Herrick⁶⁻⁹ in 1912 and again in 1918 and 1919 to describe sudden obstruction of the coronary arteries and to establish the modern differentiation of the symptomatology from that of the angina of effort Libman¹⁰ and Levine and Tranter¹¹ contributed to the subject within the above period of Herrick's writings. Immediately following that the literature in this country began to grow, bringing into relief the clinical features as seen by many men, until Christian¹² in 1925 called cardiac infarction "an easily diagnosable condition." Levine's¹³ monograph of 1929 has become a vade-mecum for students of the heart.

Aside from the characteristic pain with its duration greater than that in angina pectoris, certain features have become recognized as indicative of acute muscle damage, i.e. of the infarction caused by the abrupt continued interference with an adequate or near-adequate blood supply to the affected portions of the myocardium.

Occlusion of the smaller coronary branches has received much consideration as a cause on the one hand of precordial pain, and on the other hand of the small scars so often found at autopsy associated with atheromatous coronary vessels. While the pain alone may be indicative of deprivation of blood supply to an area at that time, it is not sufficient for the final diagnosis of infarction. If the damaged area is too small to cause such responses as leukocytosis, pericarditis, mural thrombosis, characteristic lowering of blood pressure or abrupt and progressive changes in the electrocardiogram, it is more than probable that the heart wall will heal without yielding at that particular site to intra-cardiac pressure. Qualification is necessary in that, as pointed out by Wearn,¹⁴ the classical signs may not appear when infarction occurs in the presence of heart failure. However, the adequate treatment of the failure in such a case requires protracted rest periods, and the serious error of a too short control is not likely to occur. The small scars, usually multiple, disseminated, and sometimes very numerous, still await actual demonstration by pathologists of the relation of each scar to an area of occlusion in the vessel. Scarring may be inferred clinically when persisting damage to conduction paths is demonstrated by electrocardiographic methods, but to diagnose the process in the presence only of myocardial inadequacy is still precarious. This is particularly true in hyperpiesia where in late stages severe dilatation and decompensation, with marked alteration of the complexes in the electrocardiogram, often occur without scars being found at autopsy. The intimate relation between coronary sclerosis and the smaller areas of myocardial fibrosis makes the former a widely accepted cause of the latter, but controversy will continue until more conclusive evidence clinically and pathologically is at hand.

Embolism of coronary vessels, first described by Virchow¹⁵ has been recently reviewed by Saphir.¹⁶ Its rarity, immediate fatality, and possibility of clinical diagnosis only by inference if survival should occur make consideration here unnecessary.

When gross infarction results from sudden closure as with thrombosis in a coronary vessel, the initial disturbances such as the pain with or without shock-like phenomena in the circulation, are so striking as to divert attention from the other features. Unless, however, careful attention is paid to these, which may be called the non-painful features of coronary occlusion, the opportunity to recognize actual infarction may be missed. Furthermore, the whole picture of sudden coronary occlusion may be so closely copied by certain other conditions that only painstaking study can differentiate them.

An appraisal of not only the painful, but the non-painful features is necessary if accurate diagnosis is to be made, and if we are to take further steps in determining during life whether actual necrosis of a considerable or important part of the heart wall has occurred.

Fever and leukocytosis are two signs of infarction which present whenever this process occurs in any considerable amount anywhere in the body and are the two features aside from the pain most certain to occur with the infarction of coronary thrombosis.

Fever is occasionally lacking and seldom exceeds 102° F by rectum. It is usually nearer 101 to 101.5° , is irregular in its development from day to day, begins early as a rule, varying from three to four hours to two days after the onset, and may last for from one to two weeks, though it is usually or often of shorter duration. Because of the shock-like character of the onset in many cases, mouth temperatures do not reveal the fever and Levine's insistence on rectal temperature readings as a routine is well taken.

Leukocytosis likewise is rarely absent, but is seldom or never extreme, figures of 10,000 to 16,500 being the more common and 22,600 the upper limit I have observed. A leukocytosis of 25,000 or more is reported by Levine (loc cit). P. D. White¹⁷ states that the count may rise to 30,000. Leukocytosis may be found very early, it was seen in two of our cases as early as two and three hours after the onset of pain, and has been reported by Libman and Sacks¹⁸ in one case as occurring one and one-quarter hours after the onset. The count may be elevated for from three or four days to one and even two weeks. What may be the factors preventing leukocytosis in the occasional though rare case, remain unknown. I have not found it entirely absent throughout the early days in any case of acute infarction coming to autopsy in which an adequate clinical study with repeated counts had been made. I have gained the distinct impression, formed through long observation of recovered cases as well as of autopsies in fatal cases, that the most important factor in temperature elevation and especially in the height of the leukocyte count, is the size and surface extent of the infarcted area. That this factor is determined as much or more by the character of collateral and possible Thebesian circulation in each individual as by the site of occlusion has become apparent.

The blood pressure is nearly always lowered as compared to previous levels in the individual. If it is found only slightly above normal or if it is within the normal range, and if records of previous pressures are inadequate

or unavailable, the fact that there is a drop may not be recognized at first. Periodic elevations, or elevations later during convalescence may be suggestive of previous arterial hypertension, or there may be an enlarged forcible apex beat displaced to the left, together with the percussion outline and roentgen-ray silhouette typical of the left ventricular hypertrophy which accompanies it. In several instances I have seen the blood pressure remain down near the newly acquired levels, when hypertension previous to the occlusion had been known to exist, but with recovery usually the pressure returns, to or toward the former basal levels.

The drop in blood pressure may be extreme, or it may not at first be marked, but lowering may develop in 10 or 12 hours to two days or even later, and may reach its lowest levels from two to four days after the onset of symptoms. I have watched a case in which the readings became lowest on the third day and although variable remained near 70 systolic and 60 diastolic for four days, gradually to rise later to near normal. A drop as marked as this is not common, but figures near 90 systolic and 75 to 80 diastolic pressure are frequently noted in our records. In cases furnishing evidence of previous hypertension these low levels are seldom reached, but the low pulse pressure is often noted.

The pericarditis which develops following coronary infarction is seldom accompanied by demonstrable effusion. A patch of epicardial roughening with fibrinous deposit will cover the region where an infarct reaches the surface. The clinician will find a friction rub in proportion to the frequency with which he listens during the first two to three weeks, for the rub may be very evanescent. In two cases I heard the characteristic and unmistakable sounds only once in repeated observations. When heard more persistently, which is the rule, they may appear and disappear over a period of a week or more. Accumulated experience shows that the rub is heard in only one of seven or eight cases. Levine notes it as heard in 13.8 per cent of his series. When pericarditis develops over any area except the anterior surface of the heart it is of course, inaccessible to auscultation. The fibrinous exudate is aseptic and does not spread beyond the area in which tissue damage reaches the epicardium. The amount of fluid free in the pericardial sac, though often increased is not enough for clinical recognition. That the absence of demonstrable effusion may be important in diagnosis is illustrated by the case of a man 46 years of age, free from arthritic symptoms, with sudden precordial pain, fever to 101.8° F, leukocytosis to 14,500 and with progressive changes in the electrocardiographic tracing from time to time. These features, including the age, led to the impression at first of coronary infarction. This was strengthened for a brief time when a pericardial friction rub was heard, but the spread of the rub over the entire ventral surface of the heart and the development of a large pericardial effusion caused a revision of this opinion and the final diagnosis of rheumatic carditis was confirmed by autopsy at a much later time.

Intracardiac thrombosis occurs when the infarction reaches the endocardium. The occurrence is signalled in life only by embolic phenomena. The expression of these is not always clear and unequivocal. An area of infarction anywhere in the body, if the area is large enough, will cause fever and leukocytosis as a rule. The signs of lodgement in brain, spleen, kidneys, lungs and other viscera are generally recognized. Routine and persistent search for these signs often gives crucial evidence which would otherwise be missed. The signs of embolism in so-called silent areas of the brain are difficult to interpret. A habit of recording on first examination the character and location of each individual peripheral pulse has enabled me to recognize the embolic character of phenomena in legs and forearms which would otherwise be less definitely recognizable. The radial and ulnar, posterior tibial and dorsalis pedis arteries are known to be frequently anomalous in their course, with resulting absence of pulsation at the usual sites. They are likewise frequently the site of embolism. The disappearance of a pulse in a single vessel known to be previously pulsating, when accompanied by corresponding circulatory changes in the area, is the most convincing clinical evidence of occlusion we possess. The pain, swelling and degree of color change of the part may be minimal and insufficient in themselves for the diagnosis of embolism. If, however, the observer has proof that the absence of a pulse is due not to the anomalous course of a vessel, but to disappearance of the pulse, then the diagnosis of a pathological closure rests on solid ground.

The electrocardiographic changes expressive of muscle damage are the subject of an extensive literature. Changes seen in the electrocardiogram vary from striking and distinctive, characteristic on occasion of the artery involved, i.e. whether right or left coronary, to changes which are minor and indeterminate. For this reason tracings should be taken at the earliest time possible, and should be repeated every two to four days at first, and at longer and suitable intervals later in the course. A routine health examination which includes an electrocardiogram furnishes an excellent basis for comparison. I have been fortunate in a number of cases in having on hand tracings taken before the infarction. The most definite type of electrocardiographic evidence is that derived when frequent, successive tracings show conclusive differences, for then we have evidence not only of muscle damage but of progressive change.

There is promise that the number of cases, now estimated at 15 to 20 per cent, in which no change is found when using the conventional arm and leg leads, will be greatly reduced by the use of antero-posterior chest leads, a method especially studied by Wood and his associates^{19, 20}

Certain familiar features of the clinical examination may or may not appear, and may give weight to the diagnostic conclusions. They are the shock-like condition and appearance of the patient in the early stages of the infarction, persisting for days in some, altered and often dull or distant heart tones, a gallop rhythm, signs of congestive failure, including changes

noted in the urine, dyspnea, Cheyne-Stokes respiration and the modifications of it often called paroxysmal dyspnea, acute emphysema of the lungs, and finally but of extraordinary interest and importance, changes in rate and rhythm of the heart

Precordial pain alone is not adequate for the diagnosis of cardiac infarction. There is a group of cases, considerable in number, with pain of the same character as that occurring with infarction, in whom none of the other major signs develop. Without fever or leukocytosis, the blood pressure changes, pericarditis or embolic sequelae, and with no successive changes in the form of the electrocardiogram we may suspect sudden closure of a small branch or twig. If this has in fact occurred in such a case the danger of the sequences of gross thrombosis is minimal or absent and prolonged periods of rest are not needed. In fact, the management is essentially that of the other underlying arterial and myocardial conditions inferred or actually diagnosed. Conditions other than infarction can, however, occur and be indistinguishable by the pain alone. P. N., a strong healthy man of 54 years, was eating an ice at the end of lunch when seized with severe retrosternal and constricting type of pain. He was seen within a few minutes by an accomplished and experienced physician who had no doubt about a diagnosis of coronary occlusion. When seen by me at the end of a half hour my opinion was as definite as that of my colleague, that the pain and shock-like condition were typical. With morphine hypodermically in repeated doses up to a total of one-half grain, the pain subsided to disappearance in about 50 minutes from the onset, and within four hours he was feeling well and remained so. In the succeeding days the temperature did not go above 99° F, the highest leukocyte count, taken once and twice each day, was 8,900, the percentage of polymorphonuclear neutrophils always below 65. The limits of blood pressure readings were 150/82 and 120/90. Repeated electrocardiograms showed no deviations from normal complexes, and were identical on all occasions. Studies of the esophagus for lesion were negative, but a cholecystographic dye study gave typical shadows of a partially functioning gall-bladder filled with calculi of about 7 mm diameter and less. Final pathological proof is lacking as yet, but there is no reasonable doubt as to the calculus cause of this man's symptoms. This is not an isolated instance, the citation being given to illustrate the need for serious study of the non-painful features promptly and continuously following the initial events. The combination of gall-bladder disease with true anginal symptoms and with sudden coronary occlusion is not rare, and requires observations with the accumulation of much evidence for appraisal of the true values. Erroneous impressions again were given by the pain in the case of A. E., male, aged 63, seen with Dr. Norman Johnson, in which autopsy showed a ruptured aorta with extensive interstitial hematoma dissected to the base of the heart around the coronary orifices, as well as distally to the bifurcation into the common iliac arteries. Death occurred four days after onset of symptoms. Fever to 100.6° F, leukocytosis to 16,600, signs of

obstruction in right brachial and right cerebral artery were recorded. Electrocardiographic tracings taken 48 hours apart showed minor deviations from normal with inversion of T_1 in the first, and marked changes from this tracing in the second. This was satisfactory evidence of rapid changes in the myocardium. Although it had been discussed, a diagnosis of rupture of the aorta was dismissed. The error lay in failure to take a roentgen-ray film of the chest to determine, if possible, widened mediastinal shadows. The interest lies in the fact that certain of the most crucial signs such as those of arterial closure, simulating embolism and rapidly changing electrocardiographic complexes mimicking the changes seen in myocardial infarction can develop.

The cases of infarction of the heart simulating acute abdominal conditions, first brought to attention by Levine and Tranter,²¹ have become so well known that they are now feared and sometimes avoided by even the type of surgeon who makes a diagnosis by history and abdominal palpation alone. The cases with pain minimal or absent require dependence on the non-painful features for diagnosis and the value of their study is correspondingly increased.

In proportion as evidences of the phenomena associated with the initial events of infarction are multiplied, the certainty of recognition of coronary thrombosis grows. The evidence obtained may not allow a diagnosis but may leave the clinician with diagnostic impressions only. This status should be avoided if possible. No opportunity to collect evidence should be overlooked during the early stages when the evidence is obtainable.

The responsibility of the physician is very great, both to insist on adequate rest after infarction, and to avoid unnecessary time and expense on the part of the patient if no infarction has occurred.

The question as to the period of bed rest required by a patient with an infarcted heart wall receives little discussion in our literature. Rupture through the freshly infarcted area occurs most often early, i.e. in about the second week, less often as late as the third. Patients are usually in bed at least over this time but after this period practice varies widely. Experience over many years has led the writer to require longer bed rest than formerly. It is believed now that at least eight weeks are necessary if we are to minimize the likelihood of such crippling sequelae as aneurysm of the heart wall with its attendant rupture, intra-aneurysmal thrombosis and general interference with good function of the remaining muscle. This requirement is a minimum and is increased if there is recurring pain, signs indicating extension of the infarcted area, persistent low blood pressure or other features suggesting delay in the firm fibrous replacement desired. When time sufficient to secure this has been given, many patients regain a gratifying degree of capacity. Not many cases with the 17 and 20 years' survival, as reported by P. D. White,²² are recognized, but recovery and years of relative usefulness are now known to be common, and can be definitely increased by prolonged and adequate rest with freedom from

strain immediately following the infarction. The basis on which this recovery rests can be only by adjustments in collateral circulation, an idea first given its true emphasis by Heirick (*loc cit*) and now expressed throughout the literature. Immediate adjustment of collateral circulation must occur if life is to continue and repair is to progress. Examination of many hearts of patients who have survived for varying periods after occlusion shows more or less increase in this collateral circulation with hypertrophy, as well as dilatation of the vessels involved. This process takes time—how much we do not yet know. The error of the physician should be on the side of safety. It is in this connection that the immediate and persistent study of the non-painful features has its greatest value. If one can be satisfied that a gross infarct does not exist the period of rest can be greatly shortened, and the three and four weeks' period in more common use suffices. It is just as necessary to avoid impressing the patient too severely with a sense of his limitations in this situation as it is to demand adequate time for healing in a case with gross infarction. Whether further degenerative change in the coronary vessels with subsequent occlusions can be prevented, and if so, how, is a matter for future determination.

Disturbances of rate and rhythm of the heart occur in association with the changes in the heart wall due to arterial occlusions. They are the subject of an extensive literature. The writer's records cover auricular premature beats, fibrillation and flutter, nodal premature beats and tachycardia, ventricular premature beats and tachycardia, bundle branch block and partial and complete block, including delay in auriculo-ventricular conduction.

Some of these, such as the tachycardias, may require prompt and specific treatment as life-saving measures in order to relieve the heart muscle of the added strain imposed. Premature beats are common without knowledge of coronary occlusion, and require treatment only when frequent or a source of anxiety to the patient. Extrasystoles and the tachycardias are to be treated by commonly accepted methods, with one exception. This refers to ventricular tachycardia. In this condition the use of digitalis should be avoided. Levine (*loc cit*) cautions against it. Davis²³ shows its disadvantages and dangers. Nathanson²⁴ in his remarkable studies on the human heart, showed that digitalis definitely prolonged the period of cardiac standstill induced by pressure on the carotid sinus. Its effect is probably the same under the circumstances considered here. Quinidine appears to be a safer drug in this particular condition. I have repeatedly seen it apparently control the tachycardia and restore normal rhythm. In one instance death occurred four days after cessation of the ventricular tachycardia and discontinuance of the drug, undoubtedly from other causes related to the infarction. H. D. Levine,²⁵ in an experimental study of cats, found that quinidine definitely inhibited the facility with which ventricular fibrillation could be produced by faradic stimulation, and suggested that the results offered a rational background for proper quinidine therapy as a method for preventing sudden death in those conditions in which ventricular fibrillation

is prone to occur. Ventricular tachycardia is generally recognized as such a condition. Quinidine is a definite poison to, as well as remedy for, the heart, and is believed to be capable in overdosage, of causing ventricular fibrillation. Hence the exquisite care needed if it is to be used properly.

The importance of conduction defects as evidenced by the electrocardiogram lies in two directions. First is the aid given in localizing the damage to the heart wall. Indirect reference to this was made by Herrick²⁶ in 1925 when he called attention in a parenthesis to the fact that "some parts of the heart are less vital, more indifferent, than others." Defects in auriculo-ventricular conduction show involvement of the septum near the junction of auricles and ventricles, while bundle branch block evidences an involvement lower in the septum after anatomical division of the conducting bundle has occurred.

The second and greater importance of conduction defects lies in the high immediate mortality when complete auriculo-ventricular dissociation occurs. Hansen²⁷ has published electrocardiograms from a case seen also by me in which complete heart block developed on the fifth day and disappeared on the ninth, although the patient died suddenly on the twelfth day. In my records of five cases of complete block accompanying myocardial infarction, four were fatal.

In this condition also prompt and proper treatment may be a life-saving measure. In the case of W H P, aged 60, the pulse stopped beating and the heart tones disappeared 12 hours after the initial pain. Within one minute a four inch sterile needle was thrust through the fourth right inter-space 1 cm to the right of the sternum and directed to the assumed position of the right auricle, 0.5 c.c. of adrenalin was injected through it. Within three seconds a radial pulse was noted, first as a single isolated beat, and after two or three seconds more the pulse assumed its usual character. Five and one-half hours later respirations ceased and pulse beat and heart tones again disappeared. The adrenalin injection with the same technic was repeated. On this occasion when the needle reached the depth it was apparent by its rhythmic motion that the heart was beating although no tones could be heard. No response to treatment occurred. Autopsy showed extensive atheromatous changes and a thrombus beginning about 2 cm. from the sinus of Valsalva, in the left coronary artery. There was a single needle puncture found entering the right auricle in its lower part. No hemorrhage from it was apparent. The effects of adrenalin have long been known. The excellent studies by Nathanson^{24, 28} show that epinephrine in its natural laevo-rotary form had a powerful effect on the impulse-initiating mechanism of the ventricles in man, and consistently prevented cardiac standstill by the induction of an idio-ventricular rhythm.

In concluding it may be said that when occlusion of a coronary artery occurs the mode of onset of symptoms may be strongly suggestive of the pathologic changes, but that diagnosis should not be considered easy. Given a patient seized with precordial pain apparently typical in character, if there

is survival of the initial events, which is probably the rule rather than the exception, immediate and continuing study of the non-painful features of the case is requisite for accurate appraisal. If, in fact, there is an area of infarction large enough to give fever, leukocytosis, pericarditis, intracardiac thrombosis or considerable changes in the ventricular complexes of the electrocardiogram, a long period of rest is advisable in order to promote firm, unyielding scarring of the area. A minimum of eight weeks is advised, this period to be extended if repair seems halted or inadequate. If the signs of infarction are lacking, less drastic restrictions are in order, and the diagnosis may be in question. Pain alone, regardless of how typical its character seems to be, is inadequate for an accurate and final diagnosis. Rheumatic carditis, pulmonary embolism, gall-bladder disease, and other lesions of the upper portion of the abdomen, and rupture of the aorta with interstitial hematoma present particular difficulties in differentiation.

Coronary occlusion may occur without pain and cause gross infarction. Study of the non-painful features gives our only clues to the diagnosis. Two of the many changes in rate and rhythm, i.e. ventricular tachycardia and heart block are of particular importance in prognosis and treatment.

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PERSONALITY STUDY IN THE PRACTICE OF INTERNAL MEDICINE *

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IN the course of a recent study of psychiatric education in 60 medical schools in the United States, Ebaugh ¹ questioned the professors of medicine as to the frequency of psychiatric problems in general medicine and found their answers to strike an average of 35 per cent Ziegler ² questioned 80 physicians in general practice in New York State as to the percentage of patients consulting them who had no very definite bodily disease as a basis for their complaints and found their answers to average about 20 per cent From these and other sources † there is good evidence that a large number of illnesses encountered in general medicine are of psychic origin Recently I have studied 200 consecutive private patients, classifying them as follows

(1) Those in whom the illness seemed to depend entirely on emotional problems,

(2) Those in whom the illness seemed in part dependent on emotional problems,

(3) Those in whom an emotional problem did not seem to enter into the cause of the illness Thirty-five per cent were placed in the first group, 35 in the second and 30 in the last Space does not permit the citation of many examples to illustrate the basis of this classification But, as an example of the first group there is the patient who undergoes repeated abdominal operations in a vain effort to get rid of pain or discomfort Everybody engaged in hospital practice has seen many such individuals The following case is a fairly typical one

A young woman at the age of 19 had her first attack of pain in the right lower quadrant At 20 the appendix was removed Six months later she had a pelvic operation because of painful menstruation At 26 she had her third operation for abdominal adhesions For the next four years she complained more or less constantly and had been in bed for considerable periods because of the pain in the right side Stricture of the right ureter was suspected but not proved and, finally, after a great deal of hospital investigation a fourth operation was performed in the belief that there was disease of the large bowel, but all organs were found normal

Here, then, was a patient who had been practically incapacitated for many years and who, during this period of time, had been repeatedly subjected to searching physical investigations and many abdominal operations What

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† Moersch,³ in an analysis of 500 consecutive patients seen at the Mayo Clinic, reported psychogenic factors of varying degree in 44 per cent, Stevenson,⁴ in a study of 150 patients presenting themselves to a gastrointestinal clinic, states that there was an important emotional problem in two-thirds of the cases, Reynolds,⁵ in a study of 935 unselected private patients encountered in the practice of internal medicine, concluded that 21 per cent were psychoneurotics

the many physicians attending her had not discovered or did not know the significance of was that this long illness began shortly after the fourth of her five sisters married and this patient thought that she would in all likelihood remain a spinster and would then endure a life of drudgery and comparative loneliness. Meek and submissive, unattractive and unintelligent, she unconsciously turned to illness when she found it impossible to compete with her sisters' superiority. Further personality studies disclosed her very immature emotional development and confirmed the opinion that the sister's marriage had precipitated an invalid reaction in this psychoneurotic individual.

How does modern medicine handle this large group of patients? As Forsyth,⁶ in a somewhat similar study of English medicine, has well stated, these patients are searchingly investigated by means of medical history, physical examination and laboratory studies, and then treated (1) as organically diseased, being submitted to unnecessary medical or surgical treatment, as in the example above cited, thus intensifying the neurotic condition, or (2) they are told that the physician does not *think* anything is the matter but with suspicion cast upon some organ or system which needs watching and care, as happens very often with regard to the symptom of fatigue and the suspicion of pulmonary tuberculosis, and (3) lastly in some instances such patients are still told that there is no evidence of organic disease and that the whole thing is "functional," "imaginary," "all in their head," or they are left with the implication that they are liars or malingerers, or referred to as "damn neurotics" with the unfortunate kind of care that must necessarily go with such a characterization. In other words the attitude of modern medicine is not so very different toward these patients from that described in 1884 by Clifford Allbutt,⁷ who said, in speaking of the visceral neuroses: "A neuralgic woman seems thus to be peculiarly unfortunate. However bitter and repeated may be her visceral neuralgias, she is either told she is hysterical or that it is all uterus. In the first place she is comparatively fortunate, for she is only slighted, in the second case she is entangled in the net of the gynecologist, who finds her uterus, like her nose, is a little on one side, or again, like that organ, is running a little, or it is as flabby as her biceps, so that the unhappy viscus is impaled upon a stem, or perched upon a prop, or is painted with carbolic acid every week in the year except during the long vacation when the gynecologist is grouse-shooting, or salmon-catching, or leading the fashion in the Upper Engadine. Her mind thus fastened to a more or less nasty mystery becomes newly apprehensive and physically introspective and the morbid chains are riveted more strongly than ever. Arraign the uterus, and you fix in the woman the arrow of hypochondria, it may be for life."

Why has there been so little progress in the handling of this class of patients? It does not seem to me that the reasons are difficult to find.

The physician of ancient times was concerned with the spiritual basis of illness but the structural concept introduced by Virchow led to the separation

of illness from the psyche of man and a consideration of disease as only a disorder of organs and cells. With this separation of disease into many different ailments came the development of specialists to attend to all of these distinct diseases. With the specialists came the introduction of instruments of precision and the mechanization of medicine began. Medicine now contented itself with the study of the organism as a physiological mechanism, impressed by blood chemistry, electrocardiography, etc., but unimpressed and, indeed, often holding in contempt the psychological background of the individual which was not considered as scientific as the results of laboratory studies. This period may, in truth, be referred to as the machine age in medicine. It is not to be denied that remarkable developments have occurred during this period of laboratory ascendancy but it also must be admitted that the emotional side of illness has been almost entirely neglected.

Even today the preparation in psychological medicine afforded our students is very inadequate in the great majority of medical schools. Ebaugh,¹ in the study already referred to, found that only 13 grade A schools give reasonably complete courses in psychiatry and that there appears to be a lack of psychiatric teaching personnel in approximately 85 per cent of the schools visited by the committee.

As a consequence of this structural and physiologic tradition in medicine a large number of physicians pride themselves upon their unwillingness to concede the absence of physical disease when dealing with an obscure illness. In discussing such a patient they are apt to say "but there must be something the matter" meaning that there must be a physical basis for the illness. And they furthermore believe that future researches along the lines of physical medicine will eventually uncover the hidden causes—infectious, allergic, endocrine or metabolic—responsible for such obscure illnesses.

Still another group of physicians are willing to believe that psychic factors have something to do with illness but they have only a vague notion of the part they play. They recognize that there is a "neurogenic factor" or a "large nervous element" present but they look upon this feature as a secondary one and probably a consequence of the physical disorder.

While freely acknowledging the relation of psychic causes to such physiologic phenomena as blushing, weeping, goose flesh, vomiting, diarrhea, etc., they nevertheless find it difficult to believe that more prolonged (chronic) disturbances of a physiologic nature can possibly be psychic in origin.

They are the physicians who remark about a patient,—“but he doesn't look neurotic,” perhaps imagining that such a patient should by his general apprehension or by evidences of physical nervousness betray the fact that neurosis is present. Their approach to the emotional problem is apt to consist of the question “Are you worried about anything?” Unfortunately most neurotics do not betray their neurosis in their appearance nor is the approach to their emotional problem so simple that the direct question—“Are you worried about anything?”—will produce material of importance.

More specifically then, what are some of the diagnostic and therapeutic

problems of the neuroses and how are they to be approached? One may conveniently choose four closely related headings for the discussion. First, failure to recognize neurosis and treating the patient as organically diseased. This happens most frequently, as already suggested, because modern clinical medicine attempts to establish the diagnosis of "functional" disease by ruling out organic disease through medical history, physical examinations and laboratory investigation. The point that I particularly wish to make is that the diagnosis of "functional" illness must be established not simply by exclusion of organic disease but on its own characteristics as well. In other words neurosis has its own distinctive features to be discovered by personality study. Only in this way can serious errors in diagnosis and treatment be avoided. If the above statement is admitted it must naturally follow that personality study is just as important in the problems of chronic illness as laboratory investigation.

This kind of an approach will do a great deal to relieve the fear of the physician that he is missing something organic because it will supply him with additional information to confirm his diagnosis of functional disease. It is perfectly true, of course, that organic disease can be overlooked and the patient treated as a neurotic, which is the reverse of the situation above mentioned. Physicians are constantly harassed by this fear of overlooking organic disease. They are of the opinion when dealing with this class of patients that the structural disease is hidden and will come to light with the passage of time. Again this may be true but in the majority of instances is not. A recent study from the Mayo Clinic is illuminating in this regard. Macy and Allen⁸ studied the records of 235 patients approximately six years after the diagnosis of chronic nervous exhaustion had been made, with the idea that if the clinical picture at the first examination was due to unrecognized organic disease, such organic disease should be detected by subsequent examinations over a period of years. The accuracy of the diagnosis proved to be about 94 per cent, which seems to indicate that this kind of functional illness, at any rate, is not due to organic disease. It is interesting to note in passing that 289 separate operations had been performed on 200 patients of the group that they studied.

The answer, therefore, to the reverse of the problem is substantially the same, careful physical studies plus personality investigation. In other words, one will not be so apt to overlook organic disease and treat the patient as a neurotic if personality study fails to reveal the background for neurosis. One may say further that it is unsafe to make a diagnosis of neurosis in an adult without evidence of a previous neurotic difficulty. The adult does not suddenly become neurotic unless he has had the background for a neurosis within him which personality investigation would reveal. I regret the necessity for continuing to stress personality investigation and saying nothing of the technic for so doing. But it is impossible to consider this large subject in any adequate manner at this time. Generally stated one may find important clues in a study of problems centering around vocational, religious,

marital and especially parent-child relationships. One point of special importance deserves consideration here and that is the relation of sexuality to neurosis. Ever since the introduction of the epoch-making studies of Freud in the application of psychoanalysis to the problems of neurosis, medicine has misunderstood his conception of sexuality. First, sexuality has been considered from the narrow view point of genitality, of course it is much more than that. And secondly it has mistakenly been believed that Freud considered these disturbances in genital activity to be the sole cause of the neuroses. This, indeed, is far from the truth. While the problem of sexuality in medicine is a very large one it may be stated for general purposes that difficulties in the sexual sphere serve as a revealing index to a neurotic personality and are to be looked upon only in that light. In other words, in much the same way that urea retention serves as an index to an approaching uremia so do disturbances in the sexual life of the individual, such as varying degrees of frigidity in the female and varying degrees of impotence in the male, serve as a reliable index to the kind of a personality that is very liable to the development of a neurosis.

The second problem of importance in the diagnosis of the neuroses has to do with the proposition of the recognition of a "nervous element" but ascribing it to a structural alteration which may have nothing to do with the psychic problem. This happens very often in women with anxiety or hypochondriacal symptoms in whom benign enlargements of the thyroid gland may be discovered. It happens frequently in regard to headache and supposed sinus disease and in many other instances too numerous to mention. The physician must always ask himself—are the organic defects revealed by physical examination sufficient to explain all of the symptoms? And the second question which naturally follows this one—what may be the meaning of the symptom from the standpoint of behavior? In this connection one can speak of the necessity for personality study in many patients who are to be operated upon. A slight operation in a patient not recognized as potentially neurotic will sometimes lead to a more severe illness and an extreme degree of invalidism.

Thus, a young woman was subjected to a lumbar puncture in the course of a complete examination to find the cause of frequent headaches. Immediately she became ill with more severe headaches, pain in the back and various bowel disturbances and remained bed-ridden for nine months. This was her infantile way of expressing her disapproval of her brother's marriage,—her only brother to whom she was closely attached and who acted in the capacity of father to the family. The slight operation acted as precipitating agent for the neurosis and inadequate psychologic understanding on the part of the physician permitted the illness to continue. She recovered when the meaning of the illness was made clear to her and shortly afterwards she married an older man.

The third problem to be discussed is more difficult and that is, when there is evidence both of organic disease and psychological factors the evaluation of the part played by each in producing the illness.

A young white man first seen in April 1933 complained of severe epigastric discomfort. The illness began one year before but there had been slight symptoms of gastric distress on occasions since puberty. Roentgen-ray studies showed a small part of the stomach herniated through the esophageal hiatus and it was believed that this anomaly explained his illness.

But it also developed that coincident with the onset of the present illness he had had an affair with a girl and (associated with circumstances that I will not take the time to discuss) he developed premature ejaculation and feared impotence. He thought of little else, repeatedly tried sexual intercourse with various kinds of women in order to prove himself potent, became depressed, had a dejected appearance and complained of stomach symptoms. So deep was his mental depression that even the anticipation of graduating from professional school, for which he had made tremendous sacrifices and to which he had always looked forward as his great objective, occasioned him no pleasure. He even considered forsaking his profession.

I advised him to discontinue attempts at intercourse until he had graduated, then we would discuss what treatment he must undergo. His stomach symptoms disappeared and his mental outlook improved somewhat in the succeeding months.

I felt that it was very difficult to evaluate the part played by somatic and psychic factors in this case but it is obvious that both are highly important in understanding the illness. Here, as previously discussed, the disturbance in his sexual activity served only as an index to a very passive and dependent kind of personality prone to develop neurotic illness. It has been very revealing in my studies of functional disorders of the gastrointestinal tract to find how often they are associated with disturbances in the sexual sphere.

Here we touch upon the fourth problem, in which studies are just beginning to be made, that is, the possible relationship of psychological disturbances to structural alteration. The viewpoint of disease bequeathed to us from the nineteenth century, which has been described earlier in the paper, could be indicated in the following formula:

cellular disease—structural alteration—physiological (or functional) disturbance

In the twentieth century this formula underwent alteration in some situations. For example in essential hypertension and vascular disease the formula could be altered to read:

functional disturbance—cellular disease—structural alteration

We are still in the dark as to what may precede the functional disturbance, as in the example just cited of essential hypertension and the resulting vascular disease. May it not be that future investigations will permit us, in some cases at least, to say that it is possible (among other causes) for a psychological disturbance to antedate the functional alteration? Then the formula would read:

psychological disturbance—functional impairment—cellular disease—structural alteration

The following case may illustrate my meaning.

A white man of 55 was referred to me from the bronchoscopic department of Temple University Hospital, February 1933, with the diagnosis, established by esophagoscopy and roentgen-ray, of preventriculosis, generally spoken of as cardiospasm. He was receiving treatments in the form of esophageal dilations.

The patient gave the usual medical history of this condition. He stated that his illness began about 8 or 10 years before and had been progressive. He had consulted many physicians. Discouraged, he had invested a large sum of money with an osteopath who had promised cure, finally, very sick and without funds, he had come to the hospital. The previous medical history did not seem to bear upon this illness.

His life situation, however, was interesting. He had been "born into the drug business" and had never known anything except the long hours and tedious work of an under-paid pharmacy clerk. He married young and five children came in rapid succession. It was a great financial struggle to look after them. About 1916 or 1917 while working very hard he had "some kind of a breakdown" during which there were nervous symptoms and he took bromides. In 1922 his oldest and favorite son, then aged 20, had just obtained an excellent job which paid well. He gave his salary to his mother and the father was overjoyed with the finally achieved prospects of economic freedom. He had always pictured a great career for this able son and had looked forward to his financial aid to help him in old age.

Without warning one morning shortly afterward he learned that this son had just secretly married. He said, "It was the greatest blow I ever received, not only because of the financial part of it but the way he did it," that is, secretly. The patient went on to say, "I felt like a child crying until its heart would break" and he placed his hand on his epigastrium to show where he felt the blow.

He could not get over this disappointment and even considered having the marriage annulled on the basis that the boy was too young to marry. It is interesting to note, however, that he, himself, had married at the same age. He harbored a great deal of resentment toward the girl's parents who, he felt, had stolen his fine son from him. It was during this period that attacks of swallowing difficulty occurred and grew more pronounced and more frequent.

A short time later further aggravation occurred. He learned that his brother in England, whom he described as a ne'er-do-well, was cheating his mother of her small legacy. He went to England, brought his mother back and she now makes her home with him. It is significant that the mother contributes her sole income to the up-keep of him and his family. In other words, while he accuses his brother of having "bled his mother" he, himself, had already borrowed money from her and now takes her weekly allowance for living expenses. His altruism in rescuing her from his ne'er-do-well brother seems questionable.

In this regard some psychic material of unconscious origin is interesting in revealing his character. He related two recent dreams. One had to do with the pulling of teeth which reminded him of an old maxim that he would lose a friend. He was very careful the following day in conducting himself so that he would not incur anybody's enmity. Then a dream followed in which he had ordered some coal and was shovelling it in the back yard when he suddenly discovered that there was a mountain of coal which belonged to him and in the dream he said to himself, how foolish of me to be purchasing this coal when I have a whole mountain of it here that belongs to me. He had been thinking prior to the dream of whether it was necessary to purchase coal to last out the winter and wanted to avoid doing so because of his stringent financial condition. He recognized the mountain of coal as representing a lot of money and in connection with it discussed the possibility of inheriting his mother's legacy. This gives even a better understanding of his attitude toward his mother and his fear that he would lose a friend (from the dream before).

The picture we get is that of a meek, submissive and dependent individual who had always worked hard without achieving success, strongly identified with his oldest son in whom he hoped to achieve the success denied himself. With his son's secret marriage came a tremendous disappointment from which he could not recover.

An interesting commentary in line with my thesis is his experience with the osteopath. He consulted him about December 1931 and was charged \$1000, which his sons had to borrow, "for the management of his case." It is interesting to consider why he felt like investing this great sum of money with the osteopath. He says "the osteopath told me that my trouble was due to a spasm arising from a shock" and the patient went on to say to me "he did not know about my son's marriage." He was much impressed by this diagnosis "because it was the first time that any doctor had suggested that shock and worry might be responsible for my trouble." He thereupon placed his entire confidence and all the money that he could raise in the osteopath's hands.

In the recital to me, accompanied by great emotion, this poor druggist made the following significant and perhaps revealing statement: "My son's marriage was a bitter pill that I could not swallow." And who can say that that was not, at least, one meaning of the illness?

I am not going to concern myself here with the question of pathogenesis in this case, nor is that the only problem that I have left untouched, even if you agree with me in the general idea that the illness is due to the disturbance in the emotional life. Why would this situation produce such an illness in this man and probably not in another? Why did it affect the gastrointestinal tract and particularly the lower end of the esophagus? These are questions upon which much light might be thrown by psychologic studies aimed at the deeper levels of the personality and having to do with unconscious mental forces, only hints of which are contained in this report. Such studies would necessitate the psychoanalytic method, the application of which to the problem of the organ neuroses is a vast subject the surface of which has only been scratched as yet.

The point of the above remarks can be briefly stated. The study and treatment of illness constitutes much more than the investigation and eradication of disease. And yet there is nothing new or startling in this viewpoint. We have heard a great deal in recent years about the study of the organism-as-a-whole but it seems to me that we have been paying only lip service to this concept. We have been led to believe that the art of the physician (having to do with his common sense or intuition) as opposed to his science, is sufficient to grasp the problems that we have been considering. It is not enough. A real understanding of mental mechanisms is necessary in order to study the emotional life in relation to ill health. In other words the physician must be able to define the specific mental factors producing the illness, rather than to be satisfied with vague generalizations about "neurogenic background." Just as we would criticize the physician of today who would call all fevers malaria, so we must criticize the physician of tomorrow who hints vaguely at nervous factors in the background of an illness and makes no effort to really understand the psychic situation.

In his "History of Medicine" Garrison states that the fundamental error of medieval medical science, as originally pointed out by Guy de Chauliac and elucidated by Allbutt, was in the divorce of medicine from surgery. He might have added that the fundamental error of modern medical science has been in the divorce of both from psychiatry.

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THE USE OF VERODIGEN (A DIGITALIS GLUCOSIDE) IN CARDIOVASCULAR DISEASE, ITS BIOLOGICAL ASSAY, AND PHARMACOLOGICAL ACTION [†]

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INTRODUCTION

THOSE who have assayed digitalis by any of the recognized biological methods are well aware of the difficulties encountered, and those who prescribe assayed products are frequently confronted with uncertain results. Consequently, any stable digitalis preparation producing the desired therapeutic effects and at the same time being sufficiently uniform in its action not to require a biological assay, would be greatly appreciated. From the long list of digitalis preparations on the market it is evident that no such ideal substance is available at the present time.

According to many reports, verodigen has been used in Europe for a number of years with apparently good clinical results, but is not generally known in this country, and certainly has not been used to any considerable extent.

After five years of clinical observation, Straub and Krehl¹ concluded that "everything that can be attained with digitalis will also be attained quickly, safely and in a suitable manner with verodigen." Furthermore, they state that "after four to five days it can usually be discontinued, because in favorable cases the ventricular as well as the arterial pulse rate will automatically become constant." In view of these claims, particularly the latter, there seems to be reason to wonder whether this special glucoside preparation has received sufficient biological and clinical study to warrant its being accepted without further question as a substitute for whole leaf preparations of digitalis. With these facts in mind, it seemed that verodigen, though not a definite chemical substance, possessed biologic properties which deserved to be more carefully investigated.

Verodigen was first isolated in 1912 by Kraft² who called it Gitalin. He was of course familiar with the previous methods of Schmiedeberg³ who prepared digitoxin in a pure crystalline form and found it to be practically insoluble in water.

Straub and Krehl¹ concluded that verodigen is a mixture which must contain not more than 5 per cent of ineffective substances. They also reported on several phases of its pharmacological action and concluded that it possessed all those properties which can be ascribed to digitalis substances in general, such as slowing the pulse, increasing the activity of the heart.

[†] Read at the Chicago meeting of the American College of Physicians, April 19, 1934. From the Robinette Foundation and the Graduate Hospital of the University of Pennsylvania in part under the Morris W. Stroud Jr. Fellowship in Cardiology, and from the Department of Pharmacology of Temple Medical School.

musculature, and altering the electrocardiogram. They also considered it superior to other digitalis glucosides in so far as its absorption is concerned, and believed its rate of elimination to be such as to produce the optimum degree of accumulation.

Mansfeld and Horn⁴ compared verodigen with a 0.5 per cent infusion of digitalis leaves and concluded that 0.8 mg of verodigen is equivalent to 100 mg of leaf. The same authors used isolated frog hearts, weakened by perfusion with a solution containing only one half the proper concentration of calcium. These hearts were restored by the use of verodigen in a manner similar to that seen after the use of digitalis infusions.

RESULTS OF BIOLOGICAL ASSAY AND PHARMACOLOGICAL STUDY

The tablets which contain verodigen for clinical purposes are composed largely of inert material to make them of proper size and may vary slightly in weight. They do not form a perfectly clear preparation in small volumes of sodium chloride solution as required for assay purposes. For these reasons the verodigen powder has been used in these experiments instead of the tablets.*

This powder has been found to be a white amorphous substance which readily dissolves in about 600 parts of cold water or salt solution, provided it is first thoroughly triturated with only a small amount of the solvent. It is also readily soluble in chloroform, ether, and alcohol. No definite melting point could be found, though all of it becomes a brownish liquid at less than 120° C. Fresh solutions, purposely made from the contents of one bottle, have been used in all cases included in this report, and hence no statement can yet be made concerning the uniformity of various lots or its stability in solution.

Frog Assay Assayed by the U. S. P. X one hour frog method, this material yields results which show about the same degree of variation as do those yielded by other digitalis preparations. By this method 0.0005 mg of ouabain, used as the standard, is the average minimal lethal dose per gram of normal frog. In a typical series of 35 frogs used in the present experiments, the average minimal lethal dose was 0.00045 mg of ouabain, or 90 per cent of the dose for normal frogs. Verodigen, administered in the same manner to a series of 45 frogs of the same lot, shows an average minimal lethal dose of approximately 0.0045 mg per gram, which would correspond to 0.005 mg per gram of normal frogs. If powdered digitalis leaves are of standard potency, the average minimal lethal dose is 0.6 mg per gram. It therefore follows according to this method, that verodigen has 120 times the potency of standard digitalis leaves. Mansfeld and Horn obtained a corresponding figure of 125.

Cat Assay Verodigen has also been assayed on one series of cats by the modified Hatcher's cat method of de Lind van Wijngaarden as recommended by Burn.⁵

* Merck & Co., Inc., kindly supplied the material for these experiments and the tablets used in the clinical study.

This method specifies that a 0.5 per cent aqueous extract of digitalis powder be used, and that the rate of intravenous injection from a burette be about one cubic centimeter per minute, adjusted so that death will occur in not less than 30 and in not more than 55 minutes. Artificial respiration is also specified, but in the present report artificial respiration has not been used in any case. Ether anesthesia was adjusted so that corneal reflexes were just negative, and special care taken to prevent obstruction of the trachea by mucus. Respiratory rate and depth remained good up to the time when the blood pressure fell to zero, which usually takes place suddenly.

In these experiments a 0.005 per cent solution of verodigen in salt solution was compared with a 0.5 per cent aqueous infusion of a standardized digitalis powder,* 0.85 gram of which was equivalent to one gram of the international standard. The results are shown in tables 1 and 2.

It will be noted that when a 0.5 per cent infusion of the equivalent of international standard powder was used in eight cats the average lethal dose per kilogram was 17.14 c.c. The average deviation from this average was 2.6 c.c. The "standard deviation" calculated according to Burn⁵ is 3.13 and is a measure of the amount of variation in the individual figures. According to Burn we may determine how far the average is likely to vary when different groups are used. His formula applied to the present series gives 1.4 as the "standard deviation of the average" and means that if other groups of cats are used the value obtained will vary from the true value less than 1.4 in two out of three groups, and more than 1.4 in one out of three groups.

TABLE I
Standard Digitalis Powder

| Cat No | Sex | Minutes required to kill | Wt of cat in kilos | C c of 0.5% infusion of standardized powder required to kill | Equivalent to c c of 0.5% infusion of international standard powder | C c per kilo of 0.5% infusion of international standard powder required to kill | Deviation from average |
|---------|-----|--------------------------|--------------------|--|---|---|------------------------|
| 114 | F | 68 | 2.75 | 50.5 | 59.4 | 21.7 | 4.56 |
| 107 | F | 43 | 2.95 | 39.0 | 45.9 | 15.6 | 1.56 |
| 118 | F | 41 | 3.2 | 32.5 | 38.2 | 11.9 | 5.24 |
| 112 | F | 42 | 3.15 | 40.5 | 47.6 | 15.1 | 2.04 |
| 111 | F | 56 | 2.64 | 48.0 | 56.5 | 21.4 | 4.26 |
| 109 | M | 53 | 3.1 | 49.5 | 58.2 | 18.8 | 1.66 |
| 105 | M | 51 | 3.05 | 40.5 | 47.6 | 15.6 | 1.56 |
| 108 | M | 46 | 3.25 | 47.0 | 55.3 | 17.0 | 0.14 |
| Total | | 400 | 24.07 | | | 137.1 | 21.02 |
| Average | | 50 | 3.01 | | | 17.14 | 2.6 |

"Standard deviation" 3.13

17.14 c.c. of 0.5% infusion is equal to 0.0857 Gm. of powder

"Standard deviation of the average" 1.4

* This powder was of lot 428 from the Laboratory of Hygiene, Department of Pensions and National Health, Ottawa, Canada. It was received via Sharp and Dohme through the courtesy of Dr J. C. Munch.

TABLE II

Verodigen

| Cat No | Sex | Minutes required to kill | Wt of cat in kilos | C c of 0.005% solution required to kill | C c per kg of 0.005% solution required to kill | Mg per kg required to kill | Deviation from average |
|---------|-----|--------------------------|--------------------|---|--|----------------------------|------------------------|
| 64 | M | 33 | 3.33 | 32.0 | 9.6 | 0.48 | 3.33 |
| 81 | F | 55 | 2.65 | 29.8 | 11.2 | 0.56 | 1.73 |
| 86 | M | 50 | 2.45 | 32.5 | 13.3 | 0.67 | .37 |
| 85 | F | 52 | 1.76 | 25.5 | 14.5 | 0.73 | 1.57 |
| 90 | F | 58 | 2.78 | 33.0 | 11.8 | 0.59 | 1.13 |
| 73 | F | 58 | 2.32 | 40.0 | 17.2 | 0.86 | 4.27 |
| Total | | 306 | 15.29 | | 77.6 | 3.89 | 12.40 |
| Average | | 51 | 2.55 | | 12.93 | 0.65 | 2.666 |

"Standard deviation" 2.46

"Standard deviation of the average" 1.21

0.00065 Gm verodigen is equal to 0.0857 Gm International Standard Powder

Therefore potency of verodigen is 132 times International Standard Powder

The same calculations applied to a 0.005 per cent solution of verodigen in six cats give an average lethal dose of 12.93 c c per kilogram, with a "standard deviation" of 2.46 and a "standard deviation of the average" of 1.21. These deviations are somewhat less than the corresponding values for the standard digitalis powder, and might be interpreted as due to a product having a more uniform action, or it may be due to the fact that verodigen is used here in a more potent concentration.

If 12.93 c c of a 0.005 per cent solution of verodigen are equal in potency to 17.14 c c of a 0.5 per cent solution of international standard digitalis powder, then verodigen is 132 times as potent as the digitalis powder. If Hatcher's figure of 0.1 mg of ouabain and the present figure of 0.65 mg of verodigen are accepted as the lethal doses per kilogram of cat, then ouabain, while not a digitalis preparation, is 6.5 times as potent on the cat's heart as verodigen.

Stability During the summer of 1932 seven cats were given various doses of verodigen intravenously under ether anesthesia. At that time interrupted injections were made from a syringe instead of a constant infusion from a burette. As compared with the assay tests on cats, as mentioned above, these earlier experiments required a much longer time and correspondingly lower lethal doses were obtained (table 3). No standardized digitalis powder being on hand at that time, no comparisons with digitalis were made. Recently it seemed advisable to repeat these experiments as nearly as possible, using verodigen powder from the same bottle which had been kept at room temperature and frequently opened, in order to determine whether any deterioration could be detected. The results thus obtained on four cats are shown in table 4, and are to be compared with the results previously obtained on seven cats as recorded in table 3.

TABLE III

Verodigen

| Date | Cat No | Sex | Wt in kg | Total dose and how given | Minutes required to kill | Mg per kg required to kill |
|----------|--------|-----|----------|--|--------------------------|----------------------------|
| 7/14/32 | 130 | F | 2 92 | 1 0 mg in 1 c c H ₂ O in one injection | 90 | 0 34 |
| 8/ 3/32 | 173 | F | 2 65 | 1 0 mg followed by 0 1 mg 150 minutes later | 175 | 0 42 |
| 8/ 4/32 | 164 | M | 2 06 | 9 × 0 1 mg at 5 minute intervals | 75 | 0 44 |
| 8/ 4/32 | 166 | M | 2 77 | 1 0, 0 1, 0 1 mg at 10 minute intervals | 210 | 0 43 |
| 8/ 5/32 | | M | 3 8 | 15 × 0 1 mg at 5 to 10 minute intervals | 220 | 0 39 |
| 10/28/32 | 177 | M | 4 0 | 16 × 0 1 mg at 1 minute intervals | 112 | 0 4 |
| 11/ 7/32 | 210 | M | 3 6 | 11 × 0 1 mg at 1 minute intervals, followed by 0 4 and 0 5 mg at 15 minute intervals | 100 | 0 56 |
| Total | | | 21 80 | | 982 | 2 98 |
| Average | | | 3 11 | | 140 | 0 43 |

TABLE IV

Verodigen (Twenty months after Table 3)

| Date | Cat No | Sex | Wt in kg | Total dose and how given | Minutes required to kill | Mg per kg required to kill |
|---------|--------|-----|----------|---|--------------------------|----------------------------|
| 4/2/34 | 136 | M | 3 13 | 18 × 0 1 mg at 6 minute intervals | 119 | 0 58 |
| 4/2/34 | 139 | M | 3 46 | 1 0, 0 6, 0 3 mg at 40 minute intervals | 103 | 0 29 |
| 4/3/34 | 123 | M | 3 74 | 0 5, 0 5, 0 3, 0 2 mg at about 30 minute intervals | 137 | 0 40 |
| 4/3/34 | 135 | M | 3 5 | 0 5, 0 5, 0 3, 0 1, 0 1, 0 1, 0 1 mg at about 30 minute intervals | 190 | 0 49 |
| Total | | | 13 83 | | 548 | 1 76 |
| Average | | | 3 45 | | 137 | 0 44 |

The average lethal dose per kilo recently obtained is 0 44 mg as compared with 0 43 mg obtained about 20 months previously. The average time required to produce death in the two groups is also essentially the same. These results indicate that no appreciable change in potency has taken place in this lot of verodigen powder during a period of about 20 months.

Attention is called here to the marked difference between average lethal doses of verodigen obtained by different methods. The de Lind van Wijn-gaarden method, by specifying that the rate of injection should be such as to produce cardiac arrest in 55 minutes or less, requires an average of 0 65 mg per kilo, whereas, if a period of 137 minutes is allowed, an average of only 0 44 mg is sufficient to produce death. This should serve to emphasize the importance of following the same method when comparisons are to be made between verodigen and any other material such as standard powder.

Effect on Pulse Rate Experiments on verodigen other than those concerned with assay determinations are now in progress, and in a few such cases results can now be stated

In various experiments on dogs and cats under ether anesthesia, a prompt and pronounced slowing of the pulse rate has been observed after intravenous injection of verodigen. If the dose is increased, the pulse becomes rapid and usually reaches a point, before death of the animal, which exceeds the normal rate. During this period of rapid heart action the pulse becomes irregular and finally ceases with the blood pressure falling to zero. This train of events corresponds to that during a similar injection of an aqueous extract of standard digitalis powder.

Effect on Isolated Frog Hearts When verodigen is perfused through an isolated frog heart the character of the effect produced is typical of digitalis action. Figure 1 illustrates such an effect as compared with that of ouabain. The heart promptly shows a more powerful contraction, which is soon accompanied by a diminished relaxation. The improvement in contractions is more pronounced in hearts which have already become weakened. The diminished diastole gradually progresses until the heart stops in systole.

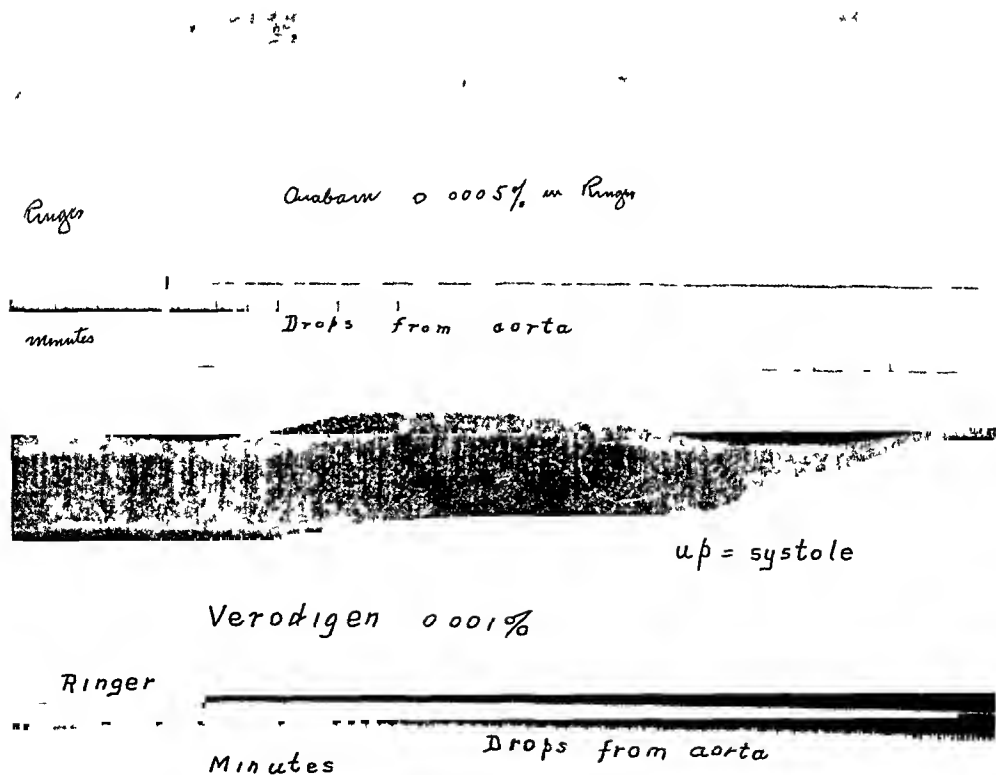


FIG. 1. The character of records obtained on isolated frog hearts by digitalis preparations. In this case ouabain and verodigen are compared.

In the experiments illustrated, the drop record from the aorta does not show an increased output in either case, although in other experiments where the action progresses less rapidly an increased output may sometimes be observed. In one experiment the output was 40 drops of Ringer's solution per minute immediately preceding the application of verodigen, increased to 52 drops during the third minute of perfusion with Ringer plus verodigen and then gradually diminished as diastole diminished.

Electrocardiographic Findings Electrocardiographic records taken on dogs after the administration of verodigen by mouth, and compared with similar records taken after the administration of digitalis leaves, show conclusively that verodigen is capable of producing a typical digitalis-like inversion of the T-wave (figure 2). At about the same time the dogs were

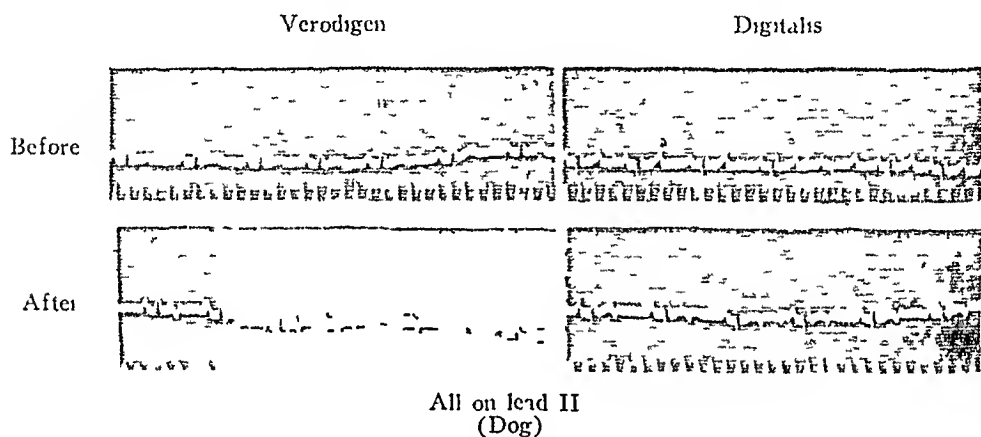


FIG 2 The inversion of the T-wave in two dogs, one of which had verodigen and the other digitalis

observed to salivate profusely, vomited, and sometimes refused food. The dose of verodigen required to elicit these symptoms was approximately 0.18 mg per kilo per day for a week. Previous to this time doses of one half this amount per day for 10 days or more had failed to produce any obvious effect.

The corresponding amount of digitalis leaves required to produce similar results was approximately 60 mg per kilo per day. It should be stated, however, that this particular lot of powdered leaf has not been assayed recently and may prove to be somewhat below the standard potency. Different dogs, or the same dog on different days, may show some variation electrocardiographically which makes caution necessary when drawing conclusions from this animal.

Absorption In one dog with a Thiry-Vella fistula 0.55 mg of verodigen per kilo introduced directly into the loop of small intestine without an anesthetic produced vomiting in 33 minutes. The pulse rate fell from 105 to 80 per minute in the same time. During the next hour vomiting occurred

five times, the pulse rate increased to 110 and became very irregular. During the next hour no changes occurred and further observations were not made. This was one of the early experiments and from later observations these symptoms would indicate the prompt absorption of an almost fatal dose.

When the lethal dose of verodigen, calculated on the basis of 0.65 mg per kilo, is given to cats by stomach tube they commonly vomit within 30 minutes and show no further marked symptoms. In a series of eight cats 80 per cent of the lethal dose, calculated in the same manner, was introduced directly into the lumen of the small intestine without a general anesthetic by opening the abdomen under local cocaine anesthesia. A syringe with large needle was used for injecting into the intestine and aseptic precautions were observed. All of these animals vomited, usually in about two hours, and one died during the following night, which indicates that verodigen is readily absorbed from the small intestine of cats. This method also shows that the vomiting is not due to local gastric irritation, unless we assume that it is regurgitated into the stomach, or eliminated into the stomach from the circulation.

Four of these cats were given verodigen the next day, in the same manner as used in the assay experiments, and required an average of only 0.37 mg per kilo instead of 0.65 as would probably have been required without the intestinal dose, thus indicating that approximately one half the effect from the intestinal dose was present the next day, after administration.

CLINICAL STUDIES

Method of Procedure Five patients with established auricular fibrillation, one patient with auricular flutter and two patients with regular sinus rhythm, presenting severe congestive failure, none of whom had taken digitalis previously, were studied on the wards of the Pennsylvania Hospital and the Graduate Hospital of the University of Pennsylvania. Also, 14 ambulatory patients with established auricular fibrillation, previously controlled with whole leaf preparations of digitalis or with Digalen,*⁷ were changed to verodigen and followed in the Out-Patient Department of the Pennsylvania Hospital. In four cases, the administration of digitalis was stopped for a period of two to four weeks immediately preceding the giving of verodigen. The drug was administered by mouth in tablets of 1/240, 1/160 or 1/80 grain each. Each out-patient was examined every week or two, at which time a vital capacity determination and an electrocardiogram were also made.

Results In the five cases of established auricular fibrillation, previously untreated with digitalis, verodigen brought about slowing of the ventricular rate, with elimination of pulse deficit, and marked clinical improvement after a total dosage of 1/16 to 1/10 grain as shown in table 5. Similarly, the

* The clinical courses of these patients had been followed carefully from December 1931 to the time of the present investigation, in a comparison of the therapeutic efficacy of Digalen with that of two whole leaf digitalis preparations.

two patients with regular sinus rhythm in severe congestive failure showed definite clinical improvement with that dosage distributed over five and eight days respectively (See reports of Cases 20 and 17, with figures 3 and 4)

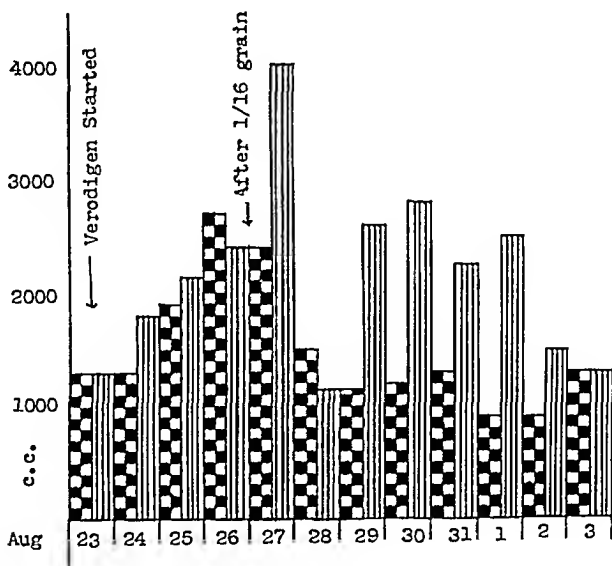


FIG 3 Case XX J G, aged 49, with arteriosclerotic hypertensive heart disease, marked cardiac enlargement and congestive failure Verodigen started after 24 hrs of bed rest Diuresis occurred on the fifth day after a total dosage of 1/16 gr Black and white sections indicate fluid intake and the vertical lined sections, the urinary output

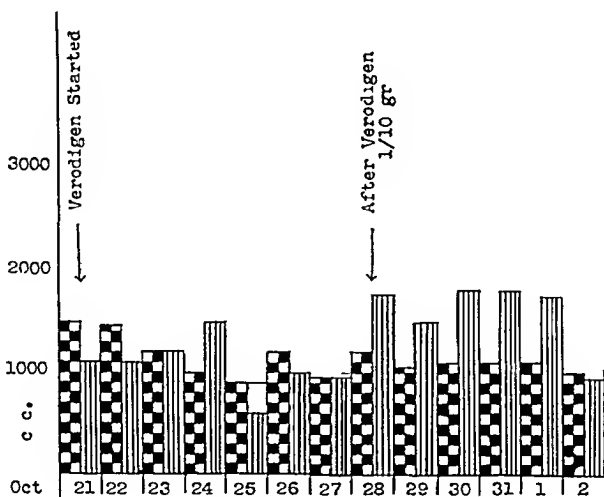


FIG 4 Case XVII G C, aged 54, with arteriosclerotic hypertensive heart disease marked cardiac enlargement and congestive failure Verodigen started after 10 days of bed rest with but little improvement during rest period Diuresis occurred on eighth day after a total dosage of 1/10 gr Black and white sections indicate fluid intake and the vertical lined sections, the urinary output

TABLE V

Summary of Cases of Auricular Fibrillation That Had Received no Digitalis before Being Given Verodigen

| Case No | Age Yrs | Sex | Etiologic classification | Cong failure | B P | Heart rate before verodigen | Heart rate after digitalization | Total verodigen necessary for full digitalization | Daily maint dose of verodigen | Period of observation, months |
|---------|---------|-----|--------------------------|--------------|--------|-----------------------------|---------------------------------|---|-------------------------------|-------------------------------|
| 18 | 36 | M | Unknown | 0 | 116/84 | 152 | 78 | 1/10 gr | 1/160 gr | 2 |
| 19 | 39 | F | Unknown (M S)* | 0 | 110/72 | 128 | 48 | 1/10 gr | 1/240 gr | 10 |
| 22 | 48 | F | Rheum F (M S) | ++ | 120/80 | 110 | 64 | 1/12 gr | 1/280 gr | 2 |
| 23 | 53 | F | Rheum F (M S) | +++ | 122/82 | 130 | 82 | 1/16 gr | 1/280 gr | 5† |
| 24 | 43 | F | Rheum F (M S) | + | 90/60 | 140 | 70 | 1/16 gr | 1/280 gr | 10 |

* M S signifies the presence of *mitral stenosis*

† Death occurred, January 4, 1934, the result of a mesenteric embolism

CASE XX

J G, an Italian male, aged 49, was admitted to the Pennsylvania Hospital, August 22, 1933, complaining of shortness of breath of six months' and edema of the legs of three months' duration. Swelling of the abdomen and orthopnea had been present for the past few days only. He had received no treatment prior to admission.

Physical examination revealed marked orthopnea and engorgement of the neck veins. The heart rhythm was regular, rate 96. The heart was enlarged almost to the anterior axillary line in the fifth interspace. A systolic murmur was audible at the apex. Moist râles were present at the lung bases, the liver edge was palpable 5 cm below the costal margin in the right mid-clavicular line, there was slight ascites, and moderate pitting edema of the lower extremities and of the lower portion of the trunk. There was moderate arteriosclerosis of the palpable vessels. Blood pressure 164/100.

On the second day after admission, the administration of verodigen was begun. On the fifth day, after having received 6 tablets of 1/80 grain each, there occurred marked diuresis (which persisted for several days), a marked slowing of the rate, and a change in the T-wave of the electrocardiogram. A daily dose of 1/80 grain was given thereafter. The patient had been up and about the ward, free from all signs of congestive failure, for 4 weeks, until October 21, when nausea and vomiting occurred.

Coupled rhythm, with ventricular premature contractions, was noticed November 21, four weeks after the administration of verodigen had been stopped, and persisted intermittently until discharge from the hospital December 30, 1933. The patient was sent home, without medication, to be followed in the Cardiac Clinic, but failed to return as advised.

Cardiovascular Diagnosis A—Arteriosclerosis, hypertension, B—Cardiac enlargement, myocardial fibrosis, mitral insufficiency, C—Regular sinus rhythm, D—Class III on admission and Class 2b on discharge from the hospital.

CASE XVII

G C, a colored male, aged 54, was admitted to the Pennsylvania Hospital, October 9, 1933, complaining of shortness of breath, swelling of the legs and fullness

in the epigastrium of two weeks' duration. Previously, he had been in fairly good health, with the exception of "asthmatic attacks" in the early fall of recent years.

On physical examination, he appeared older than the stated age. There was marked generalized arteriosclerosis, with marked cardiac enlargement and moderate orthopnea. The heart rhythm was regular, rate 116. A systolic murmur was audible at the apex. Moist râles were present at the lung bases, the liver was enlarged and tender, 9 cm. below the costal margin in the right mid-clavicular line, there was moderate ascites and pitting edema of the lower extremities. Blood pressure 165/100.

During the first 24 hours in the hospital, he was given 9 grains of powdered digitalis leaves, and then, during the next nine days, no digitalis was prescribed. At the end of that period, in spite of rest in bed, the signs of congestive failure remained practically unchanged.

On October 19, the administration of verodigen was begun. A dose of 1/80 grain was given daily until November 3. On the eighth day of this regimen, after a total of 1/10 grain of verodigen had been given, there occurred marked diuresis, which persisted for several days, with a loss of 14½ pounds in weight. Simultaneously, definite changes in the T-waves of the electrocardiogram, indicative of a digitalis effect, were present. By November 2, all signs of congestive failure disappeared, and the patient was up and about the ward without any noteworthy subjective symptoms. On November 3, a daily dosage of 1/240 grain was instituted, and was continued until his discharge from the hospital, November 21, 1933.

On January 9, 1934, he came to the receiving ward of the hospital, in extreme congestive failure, irrational and incontinent. He had failed to return to the Cardiac Out-Patient Clinic, as advised, but had returned to work and had not taken any medicine. Verodigen was administered again, but bronchopneumonia developed, and death occurred on the seventh day after admission.

Cardiovascular Diagnosis A—Arteriosclerosis, hypertension, B—Cardiac enlargement, myocardial fibrosis, mitral insufficiency (relative), C—Regular sinus rhythm, D—Class III.

CASE XXI

C. J., a negro male, aged 54, was admitted to the Pennsylvania Hospital, February 20, 1934, acutely ill, with dyspnea, palpitation and cyanosis. During the past 10 years he had suffered four attacks of palpitation with rapid heart action, associated with dyspnea and precordial pain. The duration of the attacks varied from one to 24 hours. For the past three years he had noticed shortness of breath on exertion, and, about three weeks immediately preceding admission, he began suffering marked dyspnea and tachycardia, which had grown worse gradually, with a productive cough superimposed.

Physical examination revealed orthopnea, with Cheyne-Stokes respiration and engorgement of the neck veins. The left border of the heart was in the anterior axillary line in the fifth interspace, the rhythm was regular, the rate was 170 per minute, no murmurs were audible. The radial pulse was barely perceptible. The edge of the liver was palpable 3 centimeters below the costal margin in the right midclavicular line, there were numerous moist râles at both lung bases, there was no edema of the extremities. Blood pressure 110/96. An electrocardiogram, shortly after admission, showed auricular flutter with a 2:1 auriculoventricular block.

Verodigen was given in dosage of 1/80 grain, twice daily. After four days there was improvement in his general condition, but practically no change in the heart rate. On the thirteenth day, nausea and vomiting occurred, and, therefore, the administration of verodigen was stopped. The next morning auricular fibrillation was present with a ventricular rate of 100 per minute, and the general condition of the patient was greatly improved. During the next six days no medication was given, and there occurred a gradual increase in the heart rate to 140–150 per minute, with an increasing

pulse deficit Quinidine sulphate was then prescribed On the third day of quinidine therapy, auricular flutter with 2:1 block recurred, and the patient went into a state of shock with Cheyne-Stokes respiration The administration of quinidine was stopped, and verodigen was resumed (1/80 grain, twice daily) Two days later the degree of block had changed to 3:1 and 4:1, and after another two days auricular fibrillation returned At present the patient is up and about the ward without any subjective or objective signs of circulatory insufficiency, even though auricular fibrillation persists,

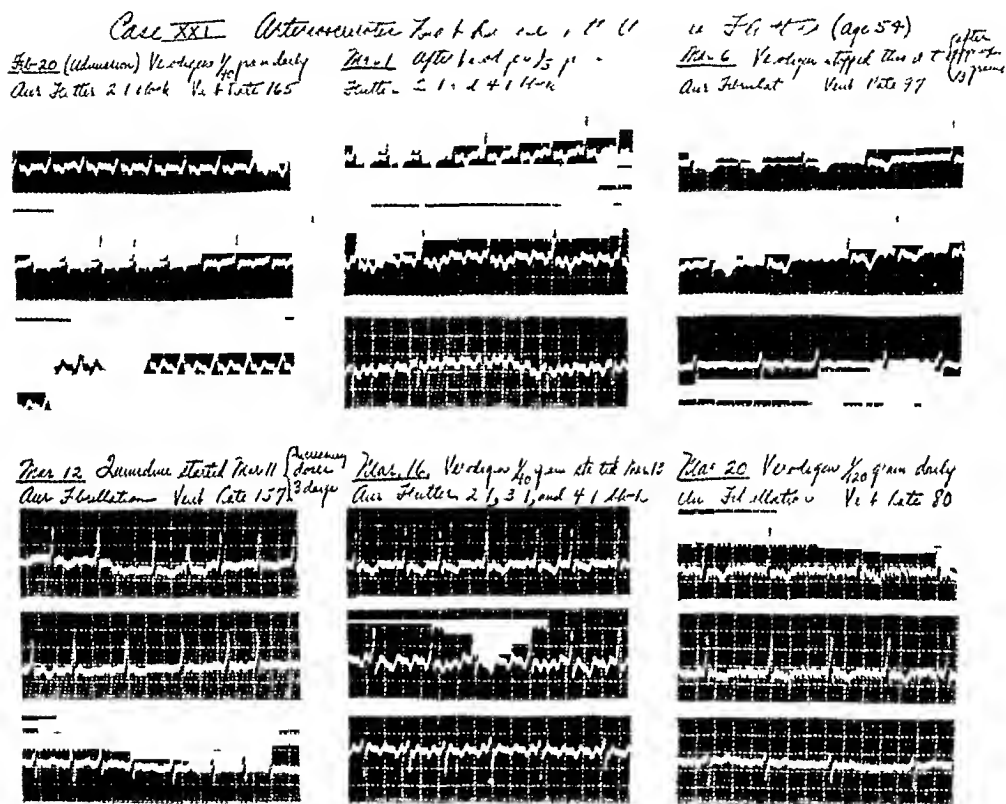


FIG 5

with a ventricular rate of about 80 per minute, with a maintenance dose of 1/240 grain of verodigen, twice daily

Cardiovascular Diagnosis A—Arteriosclerosis, B—Cardiac enlargement, myocardial fibrosis, C—Auricular fibrillation, paroxysmal auricular flutter, D—Class 2b

In the first two of the above cases changes in the T-wave of the electrocardiogram, characteristic of digitalis action, occurred simultaneously with the clinical betterment, and marked diuresis was occasioned in these cases with edema and ascites

The patient with auricular flutter and myocardial insufficiency showed a change to auricular fibrillation under the administration of verodigen, and then when medication was stopped the fibrillation reverted to flutter On resuming the administration of verodigen, fibrillation was again established

and controlled at a rate within normal range with a dose of 1/240 grain, twice daily

In 14 ambulatory patients with established auricular fibrillation, given verodigen,—after having been previously controlled for many months with whole leaf preparations of digitalis or with Digalen,—it was found that the state of optimum digitalization could be maintained without difficulty (table 6)

TABLE VI

Summary of Cases of Auricular Fibrillation That Had Been Taking Digitalis Prior to the Administration of Verodigen

| Case No | Age Yrs | Sex | Etiologic Classification | Cong failure | Vital capacity* | B P * | Cardiac area (Sq Cm)* | | Daily maint dose of digitalis† before verodigen gr | Daily maint dose of verodigen gr | Period of observation on verodigen months |
|---------|---------|-----|--------------------------|--------------|-----------------|--------|-----------------------|-----------|--|----------------------------------|---|
| | | | | | | | Actual | Predicted | | | |
| 14 | 52 | M | Unknown (M S)† | 0 | 2300 | 120/70 | 115 | 96 | B W & Co § 1½ | 1/240 | 5 |
| 4 | 32 | M | Rheum F (M S) | 0 | 2400 | 115/80 | 100 | 91 | B W & Co 1½ | 1/240 | 7 |
| 8 | 40 | M | R F (M S & A I) | + | 3300 | 120/80 | 139 | 110 | B W & Co 3 | 1/240 | 9 |
| 3 | 48 | M | Unknown (M S) | 0 | 3200 | 120/70 | 145 | 102 | B W & Co 1½ | 1/240 | 9 |
| 12 | 34 | F | Unknown (M S) | 0 | 2000 | 100/70 | 90 | 92 | B W & Co 3 | 1/240 | 11 |
| 5 | 50 | M | Unknown | 0 | 2400 | 140/90 | 112 | 103 | Digalen ‡** | 1/240 | 9 |
| 16 | 37 | M | Rheum F (M S) | 0 | 3200 | 130/70 | 147 | 103 | Digalen 1½** | 1/320 | 9 |
| 1 | 57 | M | Arteriosclerosis | + | 3500 | 130/80 | 149 | 121 | A H A 1½ | 1/240 | 9 |
| 9 | 41 | F | Unknown (M S) | 0 | 2200 | 120/78 | 117 | 100 | A H A 1 | 1/240 | 3 |
| 15 | 49 | F | Rheum F (M S) | ++ | 1200 | 110/70 | 144 | 79 | A H A 2 | 1/480 | 3 |
| 6 | 47 | F | Rheum F (M S) | 0 | 2000 | 140/90 | 136 | 90 | A H A 1½ | 1/240 | 4 |
| 7 | 37 | F | Rheum F (M S) | + | 2300 | 160/80 | 102 | 87 | A H A 3 | 1/120 | 4 |
| 10 | 29 | F | Rheum F (M S) | 0 | 1700 | 130/70 | 125 | 90 | A H A 1½ | 1/240 | 4 |
| 13 | 50 | F | Unknown (M S) | ++ | 2100 | 140/80 | 175 | 90 | A H A 1½ | 1/240 | 10 |

* The Vital Capacity, Blood Pressure, and Cardiac Area represent the *average* for each patient during the study

† With the exception of Case 1, all patients had been followed for a period of 6 to 9 months on the preparation mentioned

‡ *Unknown* signifies the absence of a history of polyarthritis and chorea, *M S* indicates the presence of *mitral stenosis*, *A I* indicates *aortic insufficiency*

§ Whole leaf tablets of Burroughs, Wellcome and Company

|| Tablets prepared by the American Heart Association

** Digalen, a "purified glucoside" prepared by Hoffman-LaRoche, Inc

An abstract of three typical cases of those included in table 6 follows

CASE XIII

B P, an Italian housewife, aged 49, made her first visit to the Cardiac Clinic of the Pennsylvania Hospital in 1924, presenting signs and symptoms of mitral stenosis and marked cardiac enlargement. Auricular fibrillation has been present since her admission to the hospital, with severe congestive failure, January 1928. Since then, she has been taking digitalis regularly. There has been a gradual diminution of her circulatory efficiency, with increasing hepatomegaly, and recently the spleen has become palpable. In spite of the cardiac handicap, she is still able to do some light housework.

Cardiovascular Diagnosis A—Unknown, B—Cardiac enlargement, mitral stenosis and insufficiency, C—Auricular fibrillation, established, D—Class 2b

Her clinical course, immediately before and during the administration of verodigen has been as follows

| Brand of digitalis | A H A | | Verodigen | | | | | |
|-----------------------------|---------|---------|-----------|--------|-----------------|---------|---------|---------|
| Date | 5/4/33* | 5/18/33 | 5/25/33 | 6/1/33 | 6/8/33 | 8/24/33 | 1/25/34 | 3/22/34 |
| Av daily dose (gr) | 1½ | 0 | 1/280 | 1/140 | 1/280 | 1/280 | 1/240 | 1/240 |
| Weight (lbs) | 135 | 136½ | 134 | 137 | 137 | 133½ | 133 | 129½ |
| Ventricular rate | 76 | 48 | 44 | 58 | 54 (Occ p c) | 68 | 76 | 72 |
| Pulse rate | 76 | 48 | 44 | 58 | 48 | 68 | 76 | 72 |
| Dyspnea | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Edema | Slight | Same | Same | Same | 0 | Slight | Same | Same |
| Lungs (râles) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liver (cm palp in m c l) | 10 | 8 | 8 | 9 | 8 | 8 | 9 | 10 |
| Blood pressure | 130/80 | 140/75 | 140/78 | 150/85 | 140/80 | 150/85 | 140/90 | 128/80 |
| Vital capacity (c c) | 2100 | 2100 | 2200 | 2100 | 2100 | 2200 | 1970 | 2100 |

* For 7 months immediately preceding May 4, 1933, this patient had been taking digitalis prepared by the American Heart Association, gr 1½, daily. On that date, she was changed to verodigen, and the next day she took two tablets, 1/80 grain each. At 5 00 a m, the morning immediately thereafter, she was awakened with vomiting and dizziness, which kept her in bed for nine days. While bed-ridden, she took no verodigen, but later on, took one tablet daily, the five days just before her next clinic visit, May 18, 1933.

CASE VIII

M K, a Hebrew salesman, aged 40, presented aortic insufficiency, mitral stenosis and insufficiency, moderate cardiac enlargement, and regular sinus rhythm on his first visit to the Cardiac Clinic of the Pennsylvania Hospital, November 1927. In August 1930, he suffered sudden loss of power in the left arm, leg and face, without loss of consciousness or speech, and two weeks were spent in another hospital. On his next visit to the Cardiac Clinic in December 1930, weakness of the left arm was the only residual finding, but auricular fibrillation was present, with a ventricular rate of 144 and a pulse deficit of 30 per minute. There were no signs of congestive failure, but he complained of palpitation and dyspnea on slight exertion. Since that time he has been taking digitalis regularly. On three different occasions, embolic phenomena have occurred in the spleen, brain and kidney, respectively, with good recovery in each instance.

Cardiovascular Diagnosis A—Rheumatic fever, B—Cardiac enlargement, aortic insufficiency, mitral stenosis and insufficiency, C—Auricular fibrillation, established, D—Class 2b.

His clinical course, immediately before and during the administration of verodigen, has been as follows:

| Brand of digitalis | B W & Co | Verodigen | | | | | |
|--------------------------|-------------|-----------|---------|---------|----------|--------|--------|
| Date | 4/20/33* | 6/15/33† | 6/29/33 | 7/27/33 | 10/26/33 | 1/4/34 | 3/1/34 |
| Av daily dose (gr) | 3 | 1/160 | 1/240 | 1/240 | 1/240 | 1/240 | 1/240 |
| Weight (lbs) | 164 | 162 | 162 | 160 | 160 | 160½ | 166½ |
| Ventricular rate | 72 | 88 | 78 | 66 | 84 | 96 | 76 |
| Pulse rate | 72 | 84 | 74 | 66 | 84 | 96 | 76 |
| Dyspnea | Slight | Slight | Slight | Slight | Slight | Slight | Slight |
| Edema | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lungs (râles) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liver (cm palp in m c l) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Blood pressure | 130/78 | 130/80 | 135/80 | 135/80 | 120/80 | 120/80 | 134/90 |
| Vital capacity (c c) | 3550 | 3400 | 3450 | 3400 | 3400 | 3400 | 3300 |

* A daily dose of 3 grains of Burroughs, Wellcome & Co's digitalis had been taken for six months prior to this date.

† Administration of verodigen started on this date.

CASE IV

S F, a Hebrew male, 32 years of age, complained of rapid heart action of three months' duration, with fatigue, dyspnea on exertion and cough, on his first visit to the Cardiac Clinic of the Pennsylvania Hospital, June 1931. At the age of 15 years, he had been told that he had a heart murmur, however, he had enjoyed excellent health and had been very active physically previous to 1931. Physical examination revealed cardiac enlargement, mitral stenosis and insufficiency, and auricular fibrillation, without any signs of congestive failure. Since that time he has been taking digitalis regularly.

Cardiovascular Diagnosis A—Unknown (tonsillitis), B—Cardiac enlargement, mitral stenosis and insufficiency, C—Auricular fibrillation, D—Class 2a

His clinical course, immediately before and during the administration of verodigen, has been as follows

| Brand of digitalis | Digalen | | Verodigen | | | | |
|-------------------------------|----------|---------|-----------|---------|---------|----------|--------|
| | 6/15/33* | 7/13/33 | 8/3/33† | 8/17/33 | 9/21/33 | 12/14/33 | 3/1/34 |
| Av. daily dose (gr.) | 1½ | 0 | 1/160 | 1/240 | 1/240 | 1/240 | 1/240 |
| Weight (lbs.) | 118 | 116 | 116 | 115 | 116½ | 118 | 120 |
| Ventricular rate | 80 | 100 | 116 | 70 | 72 | 84 | 72 |
| Pulse rate | 80 | 92 | 88 | 70 | 72 | 84 | 72 |
| Dyspnea | 0 | 0 | + | 0 | 0 | 0 | 0 |
| Edema | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lungs (râles) | 0 | 0 | + | 0 | 0 | 0 | 0 |
| Liver (cm. palp. in m. c. l.) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Blood pressure | 110/70 | 110/76 | 88/46 | 106/70 | 106/64 | 120/85 | 120/80 |
| Vital capacity (c. c.) | 2600 | 2600 | 2150 | 2600 | 2600 | 2600 | 2100 |

* Digalen, gr. 1½ daily, had been taken for a period of 8 months prior to this date. All medication was stopped on this date.

† Administration of verodigen, gr. 1/160 daily, started on this date.

In view of the potency of the preparation, it was administered to the first few patients most cautiously. Through careful check of the dosage necessary to produce therapeutic or toxic effects, it was found clinically that 1/240 grain was the approximate equivalent of 1½ grains of whole digitalis leaves (one cat unit). This figure represents a potency three times as great as that reported in the European literature (in which 1/80 grain has been termed the equivalent of 1½ grains of whole digitalis leaves).

Overdosage with verodigen produced toxic effects similar to those which might be precipitated by whole leaf preparations. In spite of the caution which attended the administration of the preparation before the approximate cat unit strength was determined, nausea and vomiting were occasioned in a few instances. In one of the two patients with regular sinus rhythm (Case 20), coupled rhythm occurred with nausea and vomiting.

DISCUSSION

The present cat assay results show verodigen to be 132 times as potent as digitalis leaf, and the frog method gives a corresponding figure of 120

These agree with a similar figure of 125 found by Mansfeld and Horn

In the present clinical studies verodigen, in doses of 1/240 of a grain, is found to produce results corresponding to 1½ grains of digitalis leaf—a ratio of 360 to 1 or nearly three times that shown biologically. This is a higher clinical potency than formerly recognized and may explain the tendency, as encountered by some cardiologists, to produce vomiting.

By the cat assay method, digitalis infusions and verodigen are both injected intravenously and hence the effect does not depend on absorption. As used clinically by mouth, if verodigen is more readily or more completely absorbed than digitalis, it would show a higher potency than digitalis. The difference, therefore, in potency as shown by the biological and clinical observations, may prove to be due to a difference in absorption. Also it must be borne in mind that there exists in the majority of patients with established auricular fibrillation a fairly wide margin between the minimum dosage necessary for optimum digitalization and the maximum dosage which can be tolerated without the incidence of toxic effects, which fact might explain in part the difference in biological and clinical observations. Furthermore, as suggested by Mansfeld and Horn, the higher potency of verodigen clinically than by the frog assay may be due to the higher temperature of man.

SUMMARY AND CONCLUSIONS

I Verodigen biologically

- 1 Is about 130 times as potent as dry standardized digitalis leaf
- 2 Slows the heart of cats and dogs as does digitalis
- 3 Inverts the T-wave of the electrocardiogram of dogs
- 4 Is promptly absorbed from the small intestine of cats and dogs
- 5 When so absorbed in large doses, about 50 per cent of the effect is present the next day
- 6 Produces vomiting which, in cats and dogs, is not due to local gastric irritation
- 7 Stops frog hearts and cat hearts in systole
- 8 As non-desiccated powder, at room temperature, is stable 20 months or more
- 9 Is soluble in water, bitter to taste, and has no definite melting point

II Clinical study

1 A clinical study of the therapeutic efficiency of verodigen—the *gitahn* glucoside of digitalis—has been made upon (a) five patients with established auricular fibrillation and one patient with auricular flutter, previously untreated with digitalis, (b) two patients with regular sinus rhythm and advanced congestive heart failure, (c) fourteen patients with established auricular fibrillation, previously controlled with whole leaf digitalis preparations or Digalen.

2 Verodigen was found (a) to control the ventricular rate in established auricular fibrillation, (b) to produce clinical improvement, with marked diuresis, in patients with congestive heart failure and regular sinus rhythm, and (c) to produce in the electrocardiogram S-T interval and T-wave changes, characteristic of digitalis action

3 Careful clinical observation revealed 1/240 gram of verodigen to be equivalent to one cat unit (approximately 1½ grains of powdered digitalis leaves)

4 The total dosage necessary for optimum digitalization varied from 1/10 to 1/16 grain, administered over a period of five to six days

5 The most frequent adequate maintenance dose of verodigen was 1/240 grain daily

6 Toxic effects from overdosage with verodigen were similar to those produced by whole leaf digitalis preparations

7 The potency of verodigen demands careful observation in its administration, especially with patients who have recently been taking any digitalis preparation

It is a pleasure to thank Dr Ernst Spiegel for taking electrocardiographic records of dogs, and Dr Ralph C Bradley for assisting in the preliminary frog assay experiments

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GLYCOGEN FORMATION IN DIABETES *

By F D W LUKENS, *Philadelphia, Pennsylvania*

DURING the past two years observations on the behavior of muscle glycogen have been made by Dr C N H Long and the author¹ at the University of Pennsylvania. The breakdown and recovery of muscle glycogen, following exercise, in normal and depancreatized animals has been directly studied and certain aspects of the formation of glycogen in the absence of insulin have been analyzed. These results will be briefly outlined and their relation to our present concepts of the mechanism of glycogen regulation in diabetes will be considered.

Since muscle glycogen comprises the largest amount of carbohydrate stored in the body, one is naturally concerned with its behavior in diabetes mellitus. Disregarding for the moment the small amounts of glycogen in the heart, kidney and skin, one may make the following summary of the glycogen content of the body. In fed animals the liver contains 6 per cent of glycogen, the muscles, 0.6 per cent. The muscle weight is more than 10 times that of the liver so that the actual quantity of glycogen is divided fairly evenly between muscles and liver. On prolonged fasting, muscle and liver glycogen diminish but not in the same proportion. Almost all the glycogen is retained by the muscles, while that in the liver is reduced to 1 per cent or often less. The fasting values are similar to those found in diabetic animals. Thus in our animals, fasted 24 hours, the normal ones had an average muscle glycogen of 727 mg per 100 gm and the diabetic of 651 mg per 100 gm, a very slight difference. No estimations were made of liver glycogen in diabetic animals but its extremely low level in such animals is an established observation. In diabetes, therefore, muscle glycogen becomes, more than ever, the chief tissue carbohydrate. It is evident that muscle glycogen is resistant to inanition or pancreatectomy in contrast to the liver which is promptly deprived of most of its glycogen under these circumstances.

From these and other such observations it is apparent that muscle glycogen is well maintained in the absence of insulin. However, only four references have been found in the literature to glycogen synthesis in diabetic animals and they disagree^{2, 3, 4, 5}. With several improvements in methods it has been possible to obtain more satisfactory results, which show directly the amount and rate of muscle glycogen formation in the absence of insulin.

There is another side to the question of glycogen synthesis. Since the discovery of insulin certain facts have been established with regard to both

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.
From the George S. Cox Medical Research Institute, University of Pennsylvania.

muscles and liver The administration of glucose raises the glycogen level in normal animals Insulin markedly increases the glycogen in diabetic animals Glucose and insulin together produce the maximum effect in both normal and diabetic animals Finally, Major and Mann⁶ have shown that merely giving glucose in large amounts to diabetic animals causes some increase in their glycogen The conclusion from this is that glycogen formation depends both on glucose concentration and on the presence of insulin Insulin affects glycogen formation, yet glycogen is formed in the absence of insulin What, then, is the relation of insulin to the process? A possible answer may be found in our direct observations upon depancreatized animals

Muscle glycogen is being built up and broken down at all times, both processes occurring simultaneously In order to study these it is necessary to interfere with the regulation or homeostasis of glycogen Exercise is the physiological means of doing this The breakdown of muscle glycogen can be so accelerated by contraction that it is readily measured The synthesis that follows can also be observed

Cats were the animals used The normal cats were fasted 24 hours before the experiments Under nembutal anesthesia both hind legs were stimulated electrically, the stimulus being the same in all experiments Immediately after stimulation one hind leg was removed, giving the glycogen level after it had been lowered by muscular contraction At the end of the recovery periods of one, two and six hours respectively, the second hind leg and a foreleg were removed for glycogen determination The technic of removal and glycogen determination has been described previously⁷ The difference between the second hind leg and the first measured the quantity of glycogen laid down during the recovery period Since resting glycogen values fluctuate considerably in the cat, and since the glycogen breakdown varies even with a constant stimulus, a resting level for the individual animal was desired This was necessary so that the amount lost during stimulation might be calculated and so that the amount recovered might be related to the amount lost For this purpose the foreleg, which was not stimulated, was taken It was found that because of its increased connective tissue the foreleg glycogen was lower than that of the hind leg, but on a number of control cats, both normal and diabetic, this was found to be a very constant difference, so that we had no hesitation in using this ratio to calculate the resting values This difference between the resting value and the value after exercise gave the amount of glycogen lost during stimulation

The diabetic cats were depancreatized one to three weeks before the experiments They were maintained on insulin until recovery from operation was complete Insulin was withdrawn 48 hours, and food 24 hours, before the experiments, which were conducted in the same manner as those on the normal animals Blood and urine sugars and D N ratios established in each instance the presence of severe diabetes

TABLE I
Muscle Glycogen (Mg per 100 Grams)

| Cat No | Rest- ing (calc) | End of Exer- cise | Decrease | | End of Re- covery | Increase | |
|---------------------|-------------------------|-------------------------|--------------------|----------------------|-------------------------|----------|---------------------|
| | | | Total | % of Rest- ing | | Total | % of Amt Lost |
| Normal Cats | | | One Hour Recovery | | | | |
| 14 | 863 | 498 | 365 | 42 | 701 | 203 | 56 |
| 15 | 845 | 325 | 520 | 62 | 541 | 216 | 42 |
| 34 | 668 | 255 | 413 | 62 | 399 | 144 | 35 |
| 38 | 974 | 553 | 421 | 43 | 773 | 220 | 52 |
| | | | Average | 52 | | Average | 46 |
| | | | Two Hours Recovery | | | | |
| 18 | 569 | 164 | 405 | 71 | 298 | 134 | 33 |
| 24 | 754 | 196 | 558 | 74 | 409 | 213 | 38 |
| 27 | 701 | 303 | 398 | 57 | 517 | 214 | 54 |
| 28 | 649 | 298 | 351 | 54 | 465 | 167 | 48 |
| | | | Average | 64 | | Average | 43 |
| | | | Six Hours Recovery | | | | |
| 40 | 715 | 197 | 518 | 73 | 614 | 417 | 81 |
| 43 | 589 | 157 | 432 | 72 | 472 | 315 | 73 |
| 44 | 624 | 97 | 527 | 85 | 417 | 320 | 61 |
| 46 | 716 | 227 | 489 | 70 | 550 | 323 | 66 |
| 89 | 779 | 248 | 531 | 68 | 514 | 266 | 50 |
| | | | Average | 74 | | Average | 66 |
| Depancreatized Cats | | | One Hour Recovery | | | | |
| 5 (5)* | 508 | 226 | 282 | 54 | 318 | 92 | 33 |
| 8 (8) | 680 | 243 | 437 | 64 | 378 | 135 | 31 |
| 9 (10) | 625 | 432 | 193 | 31 | 472 | 40 | 21 |
| 10 (8) | 545 | 406 | 139 | 26 | 475 | 69 | 50 |
| 29 (18) | 448 | 134 | 314 | 70 | 199 | 65 | 21 |
| 32 (11) | 534 | 316 | 218 | 41 | 445 | 129 | 59 |
| | | | Average | 48 | | Average | 36 |
| | | | Two Hours Recovery | | | | |
| 11 (7) | 601 | 204 | 397 | 66 | 382 | 178 | 45 |
| 17 (17) | 781 | 277 | 504 | 65 | 453 | 176 | 35 |
| 21 (16) | 646 | 222 | 424 | 66 | 414 | 192 | 47 |
| 26 (7) | 868 | 433 | 435 | 50 | 614 | 181 | 42 |
| 33 (10) | 594 | 227 | 367 | 62 | 436 | 209 | 56 |
| | | | Average | 62 | | Average | 45 |
| | | | Six Hours Recovery | | | | |
| 35 (14) | 600 | 354 | 246 | 41 | 487 | 133 | 54 |
| 37 (10) | 787 | 443 | 344 | 44 | 646 | 203 | 59 |
| 41 (12) | 694 | 297 | 397 | 57 | 390 | 93 | 24 |
| 42 (13) | 853 | 200 | 653 | 77 | 467 | 267 | 41 |
| | | | Average | 55 | | Average | 45 |

* Figures in parentheses indicate number of days after pancreatectomy

Table 1 summarizes the findings on glycogen synthesis in normal and diabetic cats at intervals of one, two and six hours after exercise. The following points are particularly noted

1 The lowering of muscle glycogen by exercise is essentially the same in normal and diabetic animals. There is no inability of the diabetic to break down glycogen on severe exercise. This agrees with the accepted facts

2 The actual amounts of glycogen laid down in the recovery period amply exceed the errors of the method (± 50 mg) and are larger than those obtained by most other workers

3 The glycogen recovery when expressed as the percentage of the amount lost is the same in the diabetic as in the normal for intervals of one and two hours

4 At six hours, however, a distinct difference is apparent. From the second to the sixth hour the normal animal has added 20 per cent of the lost glycogen to its muscles. The diabetic animal has remained almost stationary during this time. Other experiments not tabulated here have confirmed this. These consist of measurements of the synthesis occurring

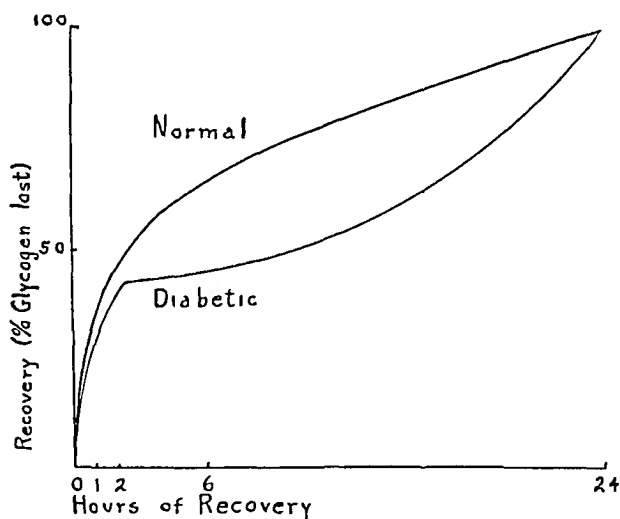


FIG 1

from the second to the sixth hour and show that there is only a trace of glycogen added by the diabetic muscles while normal ones recover almost exactly 20 per cent of the glycogen lost during stimulation

Recovery periods of 24 hours have also been used. For these only one leg was stimulated and the animal allowed to recover from the anesthetic. Twenty-four hours later a second anesthesia for the removal of the legs was performed. Here we do not have figures to show the amount lost, but calculate the glycogen in the stimulated leg in terms of the resting glycogen in the opposite unstimulated leg. At the 24 hour interval both normal and

diabetic muscles have restored their glycogen to the level of the unexercised side

Figure 1 illustrates the time relationship of glycogen resynthesis in normal and diabetic animals. It clearly shows the essential points of difference between glycogen formation with and without the presence of insulin. This consists of a delay, or slowing of the resynthesis in the later part of recovery.

Table 2 shows the blood sugars in these animals. The glucose values

TABLE II

Blood Sugar before Exercise and at the End of Recovery in Normal and Depancreatized Cats

| Normal | | | | Depancreatized | | | |
|--------|----------------------------|------------------------|-----------------|----------------|----------------------------|-------------------------------------|-----------------|
| Cat No | Period of Recovery (Hours) | Blood Sugar (Arterial) | | Cat No | Period of Recovery (Hours) | Blood Sugar (Arterial) ¹ | |
| | | Before Exercise | End of Recovery | | | Before Exercise | End of Recovery |
| 14 | 1 hour | 83 | 134 | 4 (6)* | 1 hour | 338 | 348 |
| 15 | " | 106 | 210 | 5 (5) | " | 341 | 350 |
| 34 | " | 75 | 128 | 6 (5) | " | 268 | 327 |
| 38 | " | 81 | 90 | 8 (8) | " | 338 | 302 |
| 39 | " | 92 | 166 | 9 (10) | " | 380 | 380 |
| | Average | 87 | 146 | 10 (8) | " | 358 | 365 |
| | | | | 29 (18) | " | 321 | 337 |
| | | | | 32 (11) | " | 386 | 325 |
| 13 | 2 hours | 104 | 178 | | Average | 341 | 342 |
| 23 | " | 88 | 122 | | | | |
| 24 | " | 90 | 142 | 11 (7) | 2 hours | 249 | 268 |
| 27 | " | 86 | 190 | 12 (8) | " | 226 | 313 |
| 28 | " | 120 | 89 | 17 (17) | " | 212 | 250 |
| | Average | 98 | 144 | 21 (16) | " | 258 | 250 |
| | | | | 26 (7) | " | 228 | 186 |
| 40 | 6 hours | 97 | 185 | 33 (10) | " | 276 | 260 |
| 43 | " | 67 | 123 | | Average | 242 | 255 |
| 44 | " | 83 | 118 | | | | |
| 46 | " | 80 | 116 | 35 (14) | 6 hours | 306 | 258 |
| 89 | " | 85 | 112 | 37 (10) | " | 252 | 230 |
| | Average | 82 | 131 | 41 (12) | " | 304 | 250 |
| | | | | 42 (13) | " | 358 | 312 |
| | | | | | Average | 305 | 263 |

* Figures in parentheses indicate number of days after pancreatectomy

are what one expects for normal and diabetic animals. They serve to remind us that in the diabetic glycogen is being laid down in the presence of a very high blood sugar. The work of Major and Mann previously cited shows the importance this may have as a possible compensation for the lack of insulin.

How are these facts related to our general conceptions of carbohydrate metabolism? The fact that muscle glycogen is well maintained in diabetes

agrees with all that we know on this subject, the fact that there is a retardation of the resynthesis after exercise explains certain results that have been noted. The deficiency of glycogen formation in the diabetic is one of rate. The process takes place, but more slowly than in the normal. With respect to muscle glycogen, and disregarding for the moment the other features of the disease, one must consider the possibility that in diabetes the hyperglycemia may have a compensatory influence. It follows that, in its effect on glycogen formation, insulin seems to act as a catalyst in accelerating, at a low blood sugar level, a reaction that will take place slowly at a high glucose level if the hormone is absent. This must not be taken to mean that insulin acts directly to form glycogen. In reviewing the relation of insulin to glycogen formation last year, Macleod⁸ concluded that glycogen must be influenced secondarily to other changes. This idea is compatible with our experiments. The results imply that insulin is not related directly to glycogen formation in the tissues since glycogen is formed so well in its absence.

It has been demonstrated in the diabetic animal and in severely diabetic patients that there is no elevation of the respiratory quotient during recovery from exercise. The R/Q remains at the fat level and gives no evidence of carbohydrate combustion. This may be assumed to be the case in our experiments and leads to a consideration of the possible sources of the glycogen. (1) Lactic acid and hexosephosphate may account for much that is formed during the first one or two hours. Thereafter we must consider (2) that glycogen is formed from glucose, (3) from fat, or (4) that it depends on some unknown intermediate product of metabolism. Whatever source of glycogen is postulated, the fact remains that its formation can occur independently of the oxidation of carbohydrate and in the absence of insulin. Certainly in muscle glycogen synthesis after exercise there is one phase of carbohydrate metabolism that is independent of insulin.

If other work supports these facts and implications, perhaps they will be of value as one step in a process of elimination. If the large quantity of carbohydrate held as muscle glycogen is not primarily involved in diabetes, we may have excluded one false trail in the search for the fundamental disturbance in this disease.

In transferring these results to clinical diabetes it is noted that the mechanism for muscular contraction is preserved in this condition, i.e., in the absence of insulin. The breakdown of glycogen during exercise does not differ from the normal. The subsequent restoration of glycogen occurs without the presence of insulin although the process then requires a longer time for completion. The smaller breakdown of glycogen as well as the slower recovery may explain why exercise that is not too severe and that is followed by adequate rest has been found most beneficial to the diabetic. Practically, such considerations are modified by the amount of insulin available to the individual.

To summarize, there exists in the diabetic organism a marked capacity to

maintain the muscle glycogen at about the same level as is found in fasted normal animals. A comparison has been made of the time relationships of glycogen resynthesis after exercise in normal and diabetic animals. It is concluded (a) that in the earlier phases of muscle glycogen recovery the diabetic animal is similar to the normal, (b) in the later stages, presumably involving the conversion of glucose to muscle glycogen, the normal animal shows a more rapid resynthesis, although over a 24 hour recovery period the degree of glycogen reformation is the same. The probability that this phase of carbohydrate metabolism is independent of the action of insulin and of the oxidation of carbohydrate has been discussed.

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ELECTROPHORESIS STUDIES IN CASES OF FOCAL INFECTION *

By WILLARD L. WOOD, M D,† LLOYD B. JENSEN, Ph D, and WILBER E. POST, M D, *Chicago, Illinois*

WE were encouraged to undertake an intensive study of a series of cases of focal infection because of the development of improvements in the methods of identifying sources of infection, and types of bacteria, and of determining the presence or absence of antibody formation. Certain improved methods of vaccine therapy likewise were encouraging.

We refer to the assistance that has been brought to this field of work by the determination of the cataphoretic potential of bacteria, the electrophoretic determination of the effect of serum on bacterial suspensions, and the reactions produced in obscure foci by intracutaneous or subcutaneous injections of bacterial suspensions and their products. By using these methods in studying our cases, we have had better results than in our previous experience.

The data reported here were obtained in bacteriological, biophysical, immunological and clinical studies of 215 cases in which focal infections were suspected. Our series includes 90 cases of chronic infectious arthritis (rheumatoid), 70 cases of infectious neuritis and 55 miscellaneous cases as follows: herpes zoster 8, encephalitis 5, endocarditis 8, irritable colon 5, asthma and bronchitis 10, migraine 8, chronic ulcerative colitis 2, cholecystitis 6, osteo-arthritis 3.

The cases were taken from a general medical service as they occurred in daily practice. After a history and physical examination were completed, the case was selected for study if there was any reason to suspect a focus of infection or if the study of the case from a standpoint of focal infection would lead to a more complete diagnosis.

BACTERIOLOGY AND ELECTROPHORESIS

Table 1 indicates the source of the cultures, the number taken for study (repeated cultures in many cases) and the number of cases in which streptococci were the predominating organism.

* Received for publication July 9 1934.

From Rush Medical College and medical service of Dr. W. E. Post at the Presbyterian Hospital of Chicago.

† Wilber E. Post, Fellow in Medicine at Rush Medical College, provided by Dr. Frank Billings.

TABLE I

| | No of cultures | Streptococci as the predominating organism |
|--|-------------------|---|
| 1 Tonsil crypts | 420 | 405 |
| 2 Discharge and washings from nasal accessory sinuses | 125 | 115 |
| 3 Posterior wall of the naso-pharynx | 350 | 333 |
| 4 Apices of devitalized teeth with and without x-ray evidence of peri-apical absorption | 220 | 220 |
| 5 Prostatic fluid | 70 | 40 |
| 6 Cervix of the uterus | 65 | 30 |
| 7 Anal crypts | 100 | 40 |
| Total | 1350 | 1173 |

In a limited number of cases we made bacterial examinations of bile (which was obtained with a duodenal tube), blood, urine, joint fluid and stools

The bacteria were grown in the glucose sheep's brain broth devised by Rosenow^{1,2} The tubes were incubated at 35° C for 18 hours Blood agar plates were also made of the primary material The materials for culture were inoculated into the media immediately after being obtained from the several sources

The supernatant fluid from brain broth was carefully poured into centrifuge tubes and the bacteria present were thrown down in the centrifuge A portion of the whole broth culture and of Mandler filtered broth, as well as bacterial suspensions washed in distilled water, were set aside for skin tests and for vaccine therapy if needed In no instance were secondary (transplanted) cultures used in these studies In a total of 1350 glucose brain broth cultures (excluding stool cultures) made in the study of these 215 cases, we isolated streptococci as the predominating organism in 87 per cent of the incubated broth tubes

Measurements of cataphoretic mobilities were made of these bacteria, usually streptococci, which were washed twice and suspended in conductivity water The apparatus employed in making these measurements was a modified Northrop-Kunitz-Mudd Assembly* The technic followed in this special study is reported elsewhere^{3,4} All measurements of electrical charges on the suspended bacteria were made at 140 volts, 23° C

During the course of study of these 1350 cultures of streptococci, it was observed that in certain conditions the bacteria possessed characteristic charges of negative electricity That is to say, streptococci, isolated from foci in the several diseases, could be grouped as shown in table 2, on the basis of these physical measurements

The colonies of streptococci in 10 per cent sheep's blood agar were usually of the oxidizing type, i.e., green producing A few cultures were found to be hemolytic We did not encounter many "indifferent" (non-hemolyzing-non-oxidizing) streptococci in our examination

* Arthur H Thomas Company

TABLE II

| Streptococcal suspensions from | P D (electrical charge) in mu/sec/140 volts (circa) |
|-----------------------------------|---|
| Chronic encephalitis (5 cases) | 16.6 |
| Neuritis (70 cases) | 16.6 |
| Herpes zoster (8 cases) | 16.6 |
| Chr inf arthritis (90 cases) | 25.0 |
| Endocarditis (8 cases) | 27.7 |
| Cholecystitis (6 cases) | 31.2 |
| Other miscellaneous cases | Varied widely |

SEROLOGY AND ELECTROPHORESIS

We used the methods of Shibley⁶ and of Mellon and Grenquist⁶ modified to meet our needs in studying the antibodies present in sera of patients. Serological tests usually fail to reveal antibodies in the sera of patients like those reported in this study. It appears that under suitable conditions the method of cataphoresis is useful in detecting reactions between antibodies and homologous bacteria. Should antibodies be present in a patient's serum, they unite with their specific antigen (bacterial cell). According to Northrop,⁷ the bacterial cell becomes coated with more or less antibody globulin and a lowering of electrical charge can be observed. Thus, if several series of a serum are diluted 1:50, 1:100, 1:200, 1:400, 1:800, 1:1600, 1:3200, and suspensions of bacteria (e.g., "neurotropic," "arthrotropic," etc.) are added to each row of dilutions and the tubes are then incubated at 23° C for eight hours, a union of antibody will take place with a suspension of the bacteria which is homologous to that harbored by the patient. Given a stock suspension of bacteria with a known pathogenicity and a known mobility, it is then possible to detect specific antibodies in a patient's serum. Control sera from normal persons and patients suffering from conditions other than those listed here were tested simultaneously in each set-up.

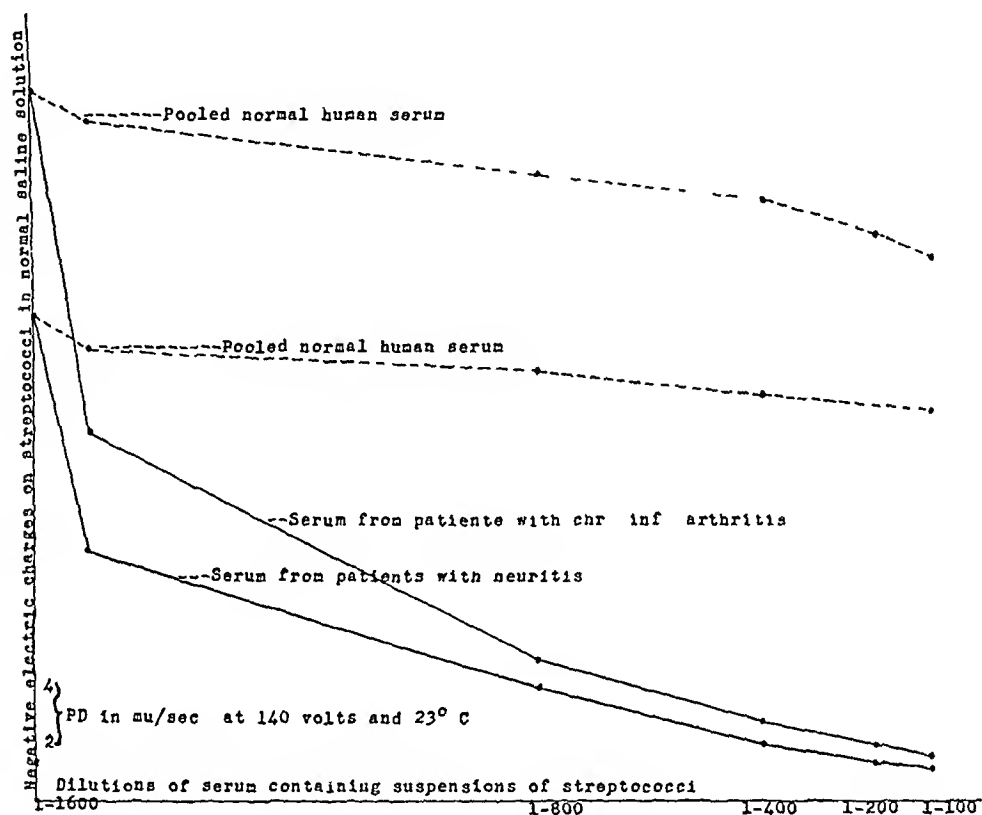
By means of these physical measurements we were enabled to differentiate conditions due to streptococcal infections from other infectious conditions. For example, an infectious arthritis of gonorrheal origin showed no antibodies specific for the test suspension of streptococci. Serum from cases of arthritis of traumatic or metabolic origin likewise showed no antibody-antigen reaction with our test suspensions. In two cases regarded as migraine we observed definite antibody-antigen reactions with suspensions of "neurotropic" streptococci. In these two cases, streptococci of "neurotropic" mobilities (16.6 mu/sec) were isolated in pure culture from the naso-pharynx. Both so-called migraine cases were relieved by establishing ethmoid sinus drainage (operative). The reaction between streptococcal suspensions and sera is shown in table 3.

METHOD OF STUDY

In all cases the eradication of possible foci was undertaken first if the condition of the patient would permit such procedure. The serum potential

TABLE III

Reaction of Normal Serum with Suspensions of Arthrotropic and Neurotropic Streptococci as Compared with Sera from Patients with Arthritis (Rheumatoid) and Neuritis



was of value here in the cases involving joints or nerve tissue, as organisms isolated from these tissues had characteristic potentials. For example, if the serum potential was positive in an arthritis case, it was classed as an infectious arthritis (green producing streptococci) and the source of the infection was sought.

The potentials of the cultures from the various sources were then taken in order to try to ascertain the focus of infection. In this manner tonsils were found to be contributory in cases where they might otherwise have been missed. In three cases of infectious arthritis the cultures from the prostatic fluid had a characteristic potential and the prostate was massaged with relief from the arthritis. Other questionable foci were studied in the same manner. If all cultures gave negative cataphoresis findings and the blood serum was positive with our stock suspension (arthritis and neuritis) the devitalized teeth were investigated and in most cases removed, even if negative in roentgen-ray films.

Roentgen-ray negative devitalized teeth were removed in 30 cases of neuritis and 20 cases of chronic infectious arthritis where the serum was

positive with our stock suspension of streptococci, after all other possible foci were eradicated. In such cases, as in all others, the apices of the teeth were cultured as described earlier. The following table gives the results obtained where both roentgen-ray negative and positive teeth were removed.

TABLE IV
Results of 220 Cultures Made from Apices of Teeth (129 Cases)

| Cases with x-ray evidence of infection | Number of cultures made | Number of positive cultures (short chain streptococci) | Number of arthrotropic or neurotropic cultures corresponding to clinical condition |
|---|-------------------------|--|--|
| <i>a</i> Neuritis | 39 | 52 | 50 |
| <i>b</i> Arthritis | 22 | 45 | 42 |
| <i>c</i> Other conditions | 18 | 40 | 5* |
| Cases with x-ray negative devitalized teeth | | | |
| <i>a</i> Neuritis | 30 | 46 | 42 |
| <i>b</i> Arthritis | 20 | 30 | 28 |
| 129 | 220 | 213 | |

* Of the 18 cases other than arthritis or neuritis, five cultures were found to be arthrotropic in character. These people gave a history of slight attacks of arthritis, but were free of symptoms at the time.

Our work compares favorably with other investigators as is shown in table 5.

TABLE V
Results of Cultures Made from Apices of Teeth

| | Number of cultures | % having 10 colonies of more | |
|------------------------------------|--------------------|--|----------|
| Haden, R L ⁸ | | | |
| X-Ray negative } devitalized | 600 | 46.2 | |
| X-Ray positive } | 500 | 62.8 | |
| Vital teeth | 400 | 4.8 | |
| Rhoads and Dick ⁹ | | % having higher counts than the controls | |
| Pulpless x-ray negative | 29 | 51.7 | |
| Austin and Cook ¹⁰ | | Positive | Negative |
| Vital teeth | 100 | 4 | 96 |
| Pulpless | | | |
| X-Ray negative | 50 | 89 | 11 |
| X-Ray positive | 50 | 94 | 11 |
| Henrici and Hartzell ¹¹ | | | |
| Vital teeth | 22 | 0 | 22 |

Skin tests were made in all cases with both the organisms and their filtrates, which will be reported later. As 160 of the patients were cases of either arthritis or neuritis, the treatment of these two conditions may be considered together. The patients were placed on cod liver oil and a high

vitamin diet, which was usually low in carbohydrates, as advised by Pemberton. Iron was given if indicated, and sunshine, heat, baths and massage were used if possible. Vaccines and filtrates were given intradermally (depending on the intradermal reaction) every five days if improvement did not follow the use of the other measures, until 10 or 15 injections had been given.

The vaccines were prepared from 18 to 24 hour primary cultures with a characteristic electrical potential, and included the products of bacterial growth which we considered important because of their usefulness in successful antibody production as found in scarlet fever therapy. The filtrate also was made from a culture of the characteristic organism in 0.2 per cent dextrose broth which was incubated seven days at 35° C. Intradermal tests were made and the bacterial suspension or filtrate was used to which the patient showed the greatest sensitivity.

Intradermal injections were made on account of the work of Besredka¹² Cannon,¹³ Kahn,¹⁴ and others, which showed that immunity could be established by intradermal injections of bacteria and their products. The filtrates were used in an attempt to obtain better results than are usually obtained from vaccines because toxins and toxoids have been used successfully for such purposes in other diseases as was shown by Dick and Dick¹⁵ in scarlet fever.

The results are summarized in table 6.

TABLE VI
Results of Treatment

| | | Free of symptoms | Definitely improved | Slightly improved | Question- able or no improve- ment |
|--|----|---------------------|------------------------|----------------------|---|
| Arthritis 90 Cases | | | | | |
| (1) Foci removed only | 10 | 5 | 3 | 2 | 0 |
| (2) Vaccine treatment | 30 | 10 | 17 | 0 | 3 |
| (3) Filtrate treatment | 40 | 15 | 18 | 3 | 4 |
| (4) Diet and hygienic measures after removal of foci | 10 | 0 | 2 | 5 | 3 |
| | | 30 | 40 | 10 | 10 |
| Neuritis 70 Cases | | | | | |
| (5) Foci removed only | 25 | 20 | 5 | 0 | 0 |
| (6) Vaccine treatment | 20 | 5 | 5 | 8 | 2 |
| (7) Filtrate treatment | 25 | 10 | 10 | 4 | 1 |
| | | 35 | 20 | 12 | 3 |

Notes on above

- (1) In five of these cases the foci were x-ray negative devitalized teeth
- (2) 20 of these cases had foci removed (12 cases with devitalized teeth x-ray positive)
- (3) 25 of these cases had foci removed (15 cases with devitalized teeth x-ray negative)
- (4) All had x-ray positive teeth removed
- (5) In 15 of these cases the foci were x-ray negative devitalized teeth
- (6) All had a focus removed (5 were x-ray negative devitalized teeth)
- (7) 12 had foci removed (10 were x-ray negative devitalized teeth)

SUMMARY

Eradication of foci is the most important factor in the treatment of arthritis and neuritis of infectious origin, as was pointed out previously by Billings and Rosenow

The methods employed increased the percentage of cases in which an active focus of infection could be identified. Roentgen-ray negative devitalized teeth are often a focus of infection.

Homologous filtrates and vaccines may be used with good results in certain cases where the patient's resistance is not too low. In many cases in which the removal of foci had not appeared to result in satisfactory improvement, good results followed the use of vaccines and filtrates.

High vitamin diets, together with accessory treatments such as light, heat, exercise, massage, sun baths and rest are always indicated as an aid in improving the patient's general condition. Vaccines or filtrates were not used unless the removal of foci and general treatment did not result in sufficient improvement.

In many cases where the foci were postnasal infections in which surgical aid was not indicated (i.e., no definite sinus involvement or not enough lymphoid tissue to justify removal), the intradermal use of a filtrate was of value.

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CONSERVATIVE TREATMENT IN OCCLUSIVE VASCULAR DISEASES OF THE EXTREMITIES

RESULTS IN 100 CASES⁴

By SAMUEL PERLOW, M D , *Chicago, Illinois*

IN the past few years the diagnosis and the treatment of peripheral circulatory diseases have received a great deal of attention in the medical literature. The methods of diagnosis have been fairly well established, but in the field of treatment, especially of the occlusive vascular diseases, there is still considerable controversy among the advocates of the various forms of therapy.

There is no specific cure for vascular occlusion of the extremities. All that we can hope to do with our present methods of treatment is to aid the development of a sufficient collateral circulation in its race with the occlusion of the primary vessels. We know that in a large number of individuals occlusion of the primary vessels takes place without the development of symptoms of ischemia because of the good collateral channels already present, and that in the majority of patients with symptoms who seek relief a sufficient collateral circulation can be established if conservative treatment is started early. Because of these facts the treatment has been ultraconservative in most clinics. Good results have been obtained with almost all of the modern forms of therapy.

In the Peripheral Circulatory Clinic of the Michael Reese Hospital we have tried to select the types of cases to be treated by the various methods. In this article we wish to report our observations as to the indications for, and our results with the different methods of treatment in 100 cases of organic occlusive vascular disease that have been under our care for six months or more.

All patients with a diagnosis of occlusive vascular disease are observed for a period of four weeks and placed on a régime consisting of rest, contrast baths and Buerger's exercise several times daily, and heat locally in the form of a baker at home. Tobacco smoking is stopped and two or three diathermy treatments of one hour each are given to both extremities weekly. At the end of this period of observation the patient is reexamined. If some improvement in the condition of the extremities has taken place, if the feet are warmer and less painful and if the patient can walk a longer distance than before, this simple treatment is continued. If there is no improvement a more radical therapy is instituted. We have found that the great majority of our cases of senile arteriosclerosis without gangrene, some cases with diabetic arteriosclerosis and a few very early cases of thromboangitis ob-

* Read at the Chicago meeting of the American College of Physicians, April 19, 1934.
From the Peripheral Circulatory Clinic of the Michael Reese Hospital.

literations will improve on this management By means of the contrast baths and the Buerger's exercise the tonus of the capillary bed, which is lost in the late stages of arteriosclerosis and in almost all cases of thromboangitis obliterans, is improved The heating of the extremity by the baker and the diathermy treatments causes a relaxation of the vasospasm which usually accompanies organic occlusion of the peripheral vessels¹ The effect of tobacco smoking on the peripheral arterial circulation has been studied by a number of authors who have shown that it will cause peripheral vasospasm and may predispose to thrombosis² In our experience tobacco smoking has been found to delay the improvement of the circulation very materially and to predispose to recurrence of the symptoms

We believe that the excellent results obtained by this therapy in a very high percentage of cases of senile arteriosclerosis but in only a few of the cases of thromboangitis obliterans can be explained by the differences in the pathology of the two conditions Arteriosclerosis is a chronic degenerative condition and the narrowing of the vessels takes place over a period of years The tissues become accustomed to the slow diminution of the blood supply so that a very slight improvement in the collateral circulation may be sufficient to restore the normal functions Thromboangitis obliterans is a more acute inflammatory disease The thrombotic process spreads continually to new vessels and there results a relatively sudden removal of the blood supply from the tissues This progressive occlusion proceeds at a more rapid rate than can be compensated by the development of the collateral circulation by the methods described

The patients that do not improve on this regime are given a more radical form of treatment such as typhoid vaccine or hypertonic sodium chloride solution intravenously If there is any contraindication to either of the above we resort to acetylcholine or tissue extract injections given intramuscularly The form of treatment used depends upon the degree of vasospasticity as determined by the vasomotor index of Brown,³ or by the nerve block method,⁴ in which the rise in temperature of the big toe is determined after anesthetization of the posterior tibial nerve with procaine

We have found that the cases with a high degree of vasospasticity will improve best on typhoid vaccine given intravenously, probably because of the fever produced and the peripheral vasodilatation The vaccine is given every five to seven days We start with 25 million of the killed bacteria (T A B) and increase by 15 to 25 million at each dose until a good febrile reaction is obtained A course of 10 to 12 injections is given and after a rest of four to six weeks this is repeated Following each intravenous injection of the vaccine there is a latent period of one to two hours This is followed by a chill which lasts for about two hours and then by a rise in the body and the skin temperatures which lasts from 12 to 72 hours The greatest objection to this treatment is the chill, which, however, has been obviated to some extent by the use of typhoid "H" vaccine Typhoid vaccine given intravenously is contraindicated in patients with myocarditis, severe arteriosclerosis, hypertension and debility

In patients with little or no vasospasticity and in whom the ischemia is due to an organic vascular occlusion only, as in marked arteriosclerosis and in late thromboangitis obliterans, hypertonic sodium chloride solution given intravenously has been of great value. We start with 150 c c of a 5 per cent solution every two or three days, and increase the dose gradually until the patient is receiving 350 c c at each injection. When properly prepared and given, the sodium chloride solution causes a flushing of the skin and a rise in the temperature of the toes of 1 to 2 degrees Centigrade without any rise in the body temperature. This local temperature increase persists for about 8 to 12 hours. We believe that the good effects of this treatment are due to the lowering of the blood viscosity and the increased blood volume which cause a more rapid blood flow through the extremities and possibly a mechanical stretching of the small blood vessels. Occasionally there is obliteration of the vein at the site of the injection when the 5 per cent solution is used. In these cases a 3 per cent solution of the sodium chloride can be used without injury to the vein. The contraindications to this form of therapy are the same as those to the typhoid vaccine.

We have used acetylcholine and tissue extract with fair results in a few cases of arteriosclerotic ischemia and thromboangitis obliterans. The acetylcholine is injected intramuscularly or subcutaneously in doses of 0.1 gram to 0.2 gram and causes a peripheral vasodilatation and a rise in the skin temperature of 1 to 3 degrees Centigrade, depending upon the degree of vasospasticity present. The rise in the temperature of the skin occurs four to six hours after the injection without an accompanying rise in the body temperature, and lasts usually four to eight hours. The acetylcholine stimulates the parasympathetic nervous system and acts as a powerful vasodilator. For this reason it acts best in cases with a marked vasospastic element. The tissue extracts seem to act in a manner similar to that of the typhoid vaccine but not as violently.

Deep roentgen therapy in the region of the lumbar sympathetic chains was given in several cases which did not improve on any of the other forms of treatment. Of the 11 cases treated two improved after a course of six treatments. The mechanism of this reaction is probably through an inhibitory effect upon the sympathetic ganglia. Others⁶ have reported similar results.

We have had very little experience with passive vascular exercise by means of external pressure changes as advised by Reid and Hermann and by Landis—not enough experience to hazard an opinion. It seems to be a logical procedure for use as an aid in the development of a sufficient collateral circulation.

One of the most important problems in the treatment of peripheral circulatory disturbances is the control of the pain which is frequently present. In the mild cases in which there is pain only on walking and in those in which there is slight continuous pain, resting the extremities in the dependent position and the use of mild sedatives are sufficient. Very often in those

patients who have pain in the extremities at night one will find that the angle of circulatory sufficiency is less than 90° . Apparently the pain is due to the cumulative ischemia and anoxemia of the tissues when the extremities are held horizontally during sleep. In such cases relief can be obtained by simply elevating the head of the bed so that the feet are below the angle of circulatory sufficiency during rest. The improvement in the circulation as a result of the various methods of treatment described above, the help of narcotics and the effects of a vasodilating drug such as nitroglycerine may together suffice to relieve the pain of even the more severe cases. However, in cases with ulceration and gangrene of the toes, more radical measures for the relief of suffering are necessary. The pain is of a severe gnawing character, is constantly present and is marked by frequent agonizing exacerbations. It may become so unbearable at times that the patients will actually beg for an amputation of the extremity. In such individuals we have found that peripheral nerve block either by injection of alcohol directly into the trunk or by crushing or cutting the nerve will give relief lasting from three to 12 months⁶. During this period conservative treatment is continued. The nerve block may be repeated if necessary.

In addition to the anesthesia following a nerve block there is in almost all cases a vasodilation and a rise in the skin temperature in the anesthetized area which may be as high as 4 degrees Centigrade. This improvement in the local circulation from nerve blocking, without other treatment, will bring about healing of long standing subungual infections and small ulcers of the toes in the majority of cases within one or two weeks after the operation. Frequently the spread of gangrene is limited and the formation of a line of demarcation is hastened.

Another minor operation which we have found to relieve pain and to improve the circulation is popliteal vein ligation. This causes a slight congestion and a dilatation of the vascular bed. It is a logical procedure in those cases of organic vascular occlusion in which only the artery is narrowed, as in arteriosclerosis. It is of no value in thromboangitis obliterans and in cases in which the communicating veins between the deep and superficial venous systems are incompetent.

COMMENT

The results obtained by conservative management in 100 cases of occlusive vascular disease that have been followed in our clinic for six months or more are shown in the accompanying table. Of 56 cases of arteriosclerotic ischemia 41 cases, or 73 per cent, improved to such an extent that they were able to return to their former occupations. Of 44 cases of thromboangitis obliterans 30 cases, or 68 per cent, improved. The duration of treatment varied from two months to two years. Twenty-nine per cent of all cases did not improve at all or have actually grown worse while under treatment. Nine per cent of all cases required amputation of an extremity.

Of these, four had ulceration or beginning gangrene when the treatment was begun

TABLE I
Results of Conservative Treatment

| Diagnosis | No Cases | Improved | | | | | | | | Not Improved* | |
|---------------------------|----------|----------|-----|-----------|---------|----------|-------|-------------|------|---------------|-------------|
| | | No | % | Diath etc | 5% NaCl | Ty-phoid | X-Ray | Nervc Block | Misc | No | Amputations |
| Arteriosclerosis | 56 | 41 | 73% | 30 | 3 | 6 | 1 | | 1† | 15 | 5 |
| Thromboangitis obliterans | 44 | 30 | 68% | 5 | 7 | 12 | 1 | 3† | 2§ | 14 | 4 |
| | 100 | 71 | 71% | 35 | 10 | 18 | 2 | 3 | 3 | 29 | 9% |

* Patients that did not improve had courses of all forms of therapy listed

† No other therapy but nerve block was used in these cases (Peripheral nerve block was performed as an aid in the control of pain in 9 other patients who then improved on the various forms of conservative treatment listed)

‡ Acetylcholine

§ Tissue extract

Our experience has been that there is a definite indication for the use of each of our present methods of conservative treatment in peripheral circulatory disturbances. The best results can be obtained by proper selection of the therapy in each case. No method is a cure in the true sense because we cannot stop the process of vascular occlusion. The patient must remain under observation indefinitely.

One of the greatest difficulties in using any of our present conservative methods is the cost. The treatment must be given over a period of months and sometimes years, and in most cases the patient cannot work during this time. For this reason the author believes that a more radical form of therapy such as sympathectomy may be justifiable on economic grounds in some of the cases. Although this operation is a very radical procedure and does not cure the vascular occlusion or stop its spread, the resulting vasodilatation gives the patient a maximum of blood supply to the extremities at all times.

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A NOTE ON THE POSSIBLE RELATION OF BLOOD GROUPS TO AGE AND LONGEVITY *

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THE purpose of this note is to point out hitherto unrecognized possibilities of blood-group investigations in relation to problems of human constitution

In 1901, K Landsteiner¹ found that blood-group formation is physiological, independent of pathological processes. This epoch-making discovery, together with the findings of E von Dungein and L Hirszfeld,² showing that groups A and B are transmitted as dominants, stimulated much additional research on the problems of serology, heredity, anthropology, paternity and constitution. The distribution of blood groups (O, A, B and AB) has been investigated in man, apes, monkeys, other mammals and in fowls, and they have been found in varying percentages in practically all human races and stocks. They are in daily use in preventing death and prolonging life through the procedure of blood transfusion, and in questionable paternity they have received recognition in the courts. In 1926, L Hirszfeld,³ in a monographic treatise, "On Constitution Serology in Connection with Blood-Group Investigations," stressed the importance of further research. There is now considerable, yet contradictory, literature on the relation of blood groups to the problems of human constitution.

Since the problems of constitution deal *primarily* with those innate characters which largely preserve individual identity, it is safe to say that only those characters which are classifiable into discernible types in the living and which, after type differentiation, remain permanent or relatively so, throughout the life span, may be useful in the problems of human constitution. The results of all investigations show that blood groups are innate and indicate that, after type differentiation early in life, the group inherited by the person remains permanent, regardless of disease and other environmental influences^{3,4}. Therefore further research on the relation of blood groups to problems of human constitution may be of great promise, although the recorded results, thus far, are contradictory. May not the reasons for such results be found in the lack of uniformity in technical details, race, stock or even community differences, inadequate numbers and controls and possibly in the fact that blood groups have not yet been studied in relation to age and longevity factors?

The relation of heredity to longevity has long been recognized and given some consideration by physicians under the heading *family history*, and this

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relation receives constant actuarial consideration. Genealogical and other studies show that longevity is heritable not only in man but in lower forms.⁶ In summing up his mathematical discussion on the relation of heredity to duration of life, Pearl⁶ states, it "indicates that from one-half to three-fourths of the death rate is selective in character, because that proportion is determined by hereditary factors. Just in proportion as heredity determines the death rate so is the mortality selective." Obviously the known relation of heredity to longevity, whatever its magnitude may be, has a definite place in the problems of human constitution. But before this relation can be useful in these problems, the types of inherited characters must be shown to remain permanent or relatively so, after type differentiation, and their possible age incidences must be investigated. *The only investigations of inherited character-types in relation to age and longevity recorded in the literature are those on human scapulae*

A brief summary of the writer's studies, based primarily on human scapulae, will indicate the possibilities of similar studies of other inherited character-types and among these, blood groups. Incident to family studies in 1906, he was led to classify the scapulae of man and some other mammals into *convex* and *scaphoid* (straight, concave and mixed) *types* (figure 1). Observing in 1907, that *convex* types predominate in the old and *scaphoid* types in the young, he was led to investigate the origin, permanence, distribution and age incidence of scapular types, as well as their possible relation to longevity.⁷⁻²¹ His investigations show that in man, the range in variation of scapular types is from the extremely *convex* through the *straight* to the extremely *concave*, their origin is primal, in man, they are transmitted with unusual constancy, regardless of sex, the *scaphoid* (straight, concave and mixed) *types* as dominants, they are differentiated in man in prenatal life, they remain permanent in type in man throughout the life span, regardless of aging processes, nutrition, health, disease, occupation and other environmental influences, they are found in varying percentages in the remains of ancient and modern man and of some other mammals (gorilla, orang, chimpanzee, armadillo, bat, et al), they are present in man in varying percentages in the excellently, well and poorly adaptable, regardless of age, race, stock and body build, in similar age periods, they may be present in varying percentages in different communities of the same race or stock, and that in healthy and sick groups, representing successive age periods from childhood to old age, the percentages of *convex* types *increase*, while those of *scaphoid* types *decrease*. His more recent figures on the age incidence of scapular types in white stocks based on approximately 15,000 grammar school and orphan asylum children and 4,000 inmates of homes for the aged are approximately as follows: six to 15 years *scaphoid* types 65 per cent, *convex* types 35 per cent, 60 years and over *scaphoid* types 35 per cent, *convex* types 65 per cent.

Since investigations in various directions, including follow-up, lead to the conclusion that scapular types remain permanent throughout the life span,

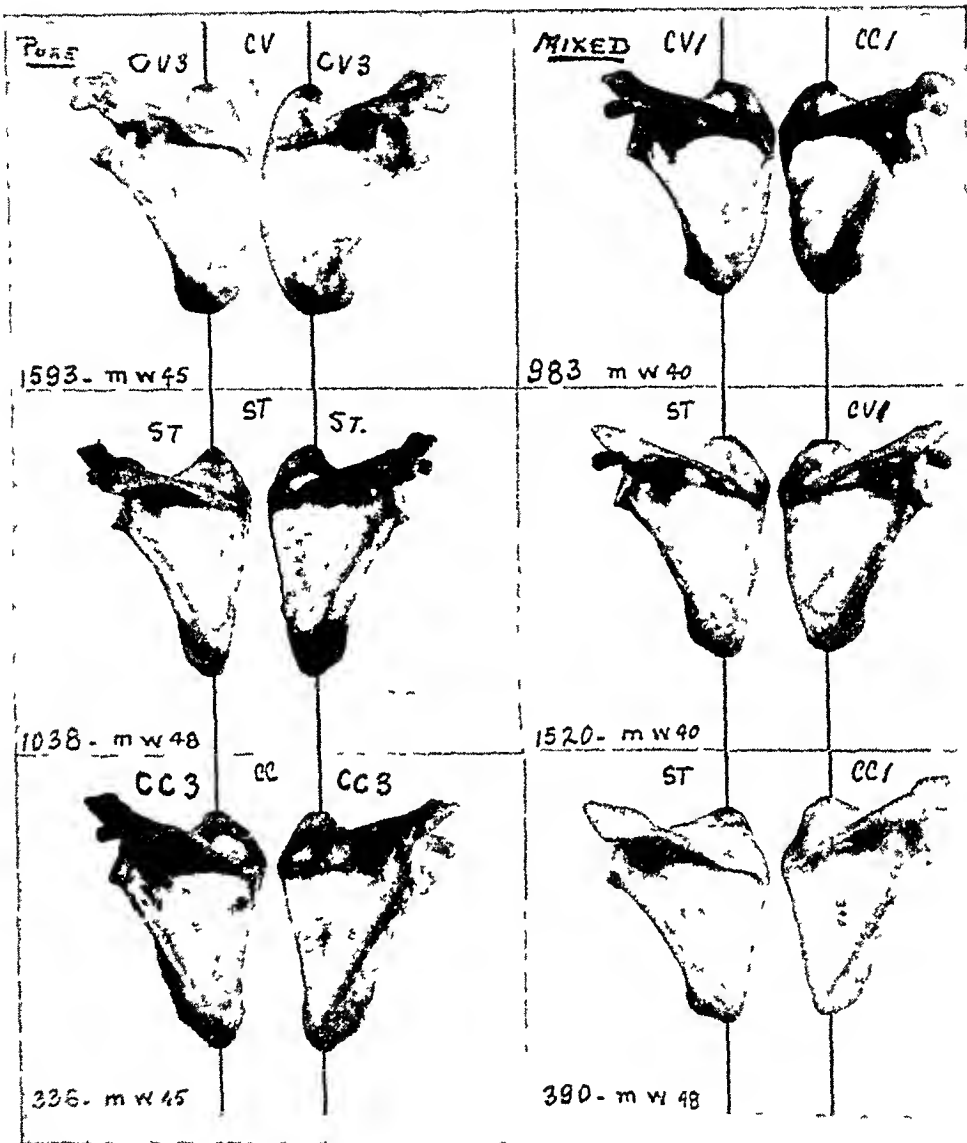


FIG 1 Photographs of six pairs of scapulae from white males in the age period 40-49 derived from dissection-room material, Laboratory of Anatomy, Western Reserve University School of Medicine, Cleveland, Ohio. The three pairs on the left (*convex*, *straight* and *concave* types) in the order named from top to bottom are typical "pure" types, i.e., each bone of each pair is of the same type. The three pairs on the right are "mixed" types (*convex + concave*, *straight + convex* and *straight + concave*) in the order named from top to bottom. "Pure" straight, "pure" concave and "mixed" types are designated *scaphoid* by the author. His classification is based *primarily* on the relation of the greater portion of the vertebral border below the scapular spine to a straight line and *secondarily* on a number of correlated characters peculiar to each type. (See reference 10.)

the only tenable explanation for their age incidence is *better adaptability, less morbidity, greater longevity among the bearers of the convex than among the bearers of the scaphoid types*. This explanation finds support in the writer's figures and in the communicated figures of others,^{13 14, 17, 19, 21} showing that in the groups studied in similar age periods there are approximately $1\frac{1}{4}$ to $2\frac{1}{4}$ times as many *convex* types in healthy groups (public school and university students, army applicants and American Expeditionary Force men) as in sick groups (feeble-minded, insane, tuberculous and prison). Whether the types of other inherited characters will show similar age incidences in relation to the problems of constitution (adaptability, morbidity and longevity) cannot be known until such types have been investigated in a similar manner.

Since blood groups had not been investigated in relation to age and longevity, and since it seemed that investigations of their possible age incidence might reveal the presence or absence of such relations, investigations were begun in 1933 by Mr H C Pulley, Assistant, Department of Bacteriology and Dr J B Mitchell, Jr, Instructor, Department of Pharmacology, St Louis University School of Medicine and Sister Mary Francis, Technician, University Hospital. The investigations of Sister Mary Francis deal with healthy and with hospitalized and out-patient material (white males and females) in successive age periods from birth onward. The results of her investigations will be published elsewhere. Those of Pulley and Mitchell are with white male freshmen and sophomores in the Medical School and ambulatory white male inmates of the St Louis Infirmary (Alms House). The results of their investigations, thus far available, arranged according to the international classification, are as follows:

| Age Period | Total | No <i>O</i> % | No <i>A</i> % | No <i>B</i> % | No <i>AB</i> % |
|---------------------------|-------|--------------------------|-------------------------|--------------------------|--------------------------|
| Fresh—Soph 22-26 Yrs ♀ | 281 | 115 40.9 | 112 39.9 | 38 13.5 | 16 5.7 |
| 60+ Yrs ♀ | 500 | 232 46.4 | 203 40.6 | 48 9.6 | 17 3.4 |
| | | Percentage Increase 13.9 | Percentage Increase 1.7 | Percentage Decrease 28.8 | Percentage Decrease 40.4 |

As far as known, the first investigations on the possible age incidence of blood groups are those of Pulley and Mitchell and those of Sister Mary Francis. Pulley's and Mitchell's results, thus far, are based on admittedly small numbers, and while the number and percentage differences in relation to age are comparable they are not conclusive, even for the age periods represented. However, the known age incidence of scapular types and its explanation suggest the possibilities of further blood-group investigations in relation to age. Such investigations by many workers with large numbers, representing healthy and sick groups of different races or stocks and

different communities of the same race or stock, may disclose definite answers to the questions Is there an age incidence of blood groups? If so, can it, like that of scapular types, be explained on the known relation of heredity to longevity? Affirmative answers to these questions will enlarge the usefulness of blood groups in relation to the problems of human constitution, as these are expressed in innate predisposition to health or disease, innate capacities for living and adaptability in general

The writer wishes to thank Mr H C Pulley and Dr J B Mitchell, Jr, for the use of their figures and to express his appreciation of the encouragement given him by Professors Moyer S Fleisher and John Auer in the effort to stimulate further research on the relation of blood groups to problems of human constitution

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THE HISTORY OF THE INVENTION AND DEVELOPMENT OF THE STOMACH AND DUODENAL TUBES *

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PRECURSORS OF THE STOMACH TUBE

UNLIKE many of our simpler medical and surgical instruments, mention of the stomach and duodenal tubes is not to be found in the classical writings of the ancient Greek and Arabian physicians. The history of the duodenal tube goes back only some 40 years while the somewhat uncertain origin of the stomach tube may be placed at about 144 years ago. Precursors of the stomach tube, however, were in common usage as early as the days of Imperial Rome.

In the time of the Emperor Claudius, it was common practice at the end of a feast or banquet to serve an emetic, the "vomition,"²² with the dessert which when effective gave a sense of well-being and permitted the partakers to straightway begin another feast. The amount of emetic given seems to have varied considerably, for often as not it produced merely an uncomfortable sense of nausea or an intractable vomiting even after the stomach became empty. Passing the finger into the posterior pharynx was another method quite commonly used by the Romans. A more refined means of emptying the stomach came in to favor with the use of the "pinna." This was a feather or group of feathers dipped in iris or cypress oil used to tickle the soft palate and posterior pharynx. Indeed, Agrippina is said to have had Claudius murdered by bribing his physician to use poisoned feathers.

During the middle ages, under different social customs the demand for agents by which the stomach could be emptied was not so great but was still present due to the popularity of poisoning as a means of murder. Oribasius recommended that a long leather glove finger, the lower end stuffed with wool, be pushed down the throat. Hieronymus Mercurialis advised the use of a long leather strip called "lorum vomitorium." This was coated with several unappetizing substances, the basis of which was tannic acid. One end of this was swallowed and the other held outside the mouth.

About the middle of the seventeenth century there appeared in Europe a new and rather curious instrument which was received in Germany very enthusiastically. Various names were given to it, such as "magenkratzer," "magenraumer," "magenburste."¹³ A rather voluminous literature extending over 90 years sprang up concerning the indications for and technic of its use. These stomach brushes constructed of whale bone arched in almost a half circle were tipped with an ivory bead and tufts of horse hair, silk or linen. Heated controversies raged at times concerning the propriety

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of their use In some localities they were publicly owned and kept in either the parish church or convent In other places their use was forbidden by law

I do not suppose we know definitely who first passed a tube into the human stomach or for what purpose, but there are many suggestive references that it was done before the time of Physick, who by most writers is credited with the invention of the stomach tube and pump in 1800 It would seem probable that such intubations were not done prior to the Dutch physician and chemist Van Helmont²² who first made flexible catheters of leather soaked in resin in 1646 Boerhave²³ (1668-1738), another Dutch physician, was the first to suggest that a flexible tube be passed into the stomach for medical purposes, but we have no record that he ever did what he recommended

In the *Philosophical Transactions* (Vol 66) appeared a paper by John Hunter, read March 21, 1776 This paper, entitled "Proposals for the Recovery of Persons Apparently Drowned," contains the following "It will certainly prove advantageous if the same kind of steams (i e, steam of volatile alkali, or warm balsams and essential oils) can be conveyed into the stomach, as that seat of universal sympathy will be aroused by such means

"Secondly a syringe with a hollow bougie or flexible catheter of sufficient length to go into the stomach, and convey stimulating matter into it, without affecting the lungs "

Whether anyone ever carried out these directions we do not know, but in 1790 this same John Hunter reported a case to the Society for Improvement of Medical and Chirurgical Knowledge as follows

"A case of paralysis of the muscles of deglutition, cured by an artificial mode of conveying food and medicines into the stomach " I will quote the description of the instrument he used as he gave it

"The instrument made use of was a fresh eel skin of rather a small size, drawn over a probang, and tied up at the end, where it covered the sponge, and tied again close to the sponge, where it fastened to the whale bone, and a small longitudinal slit was made into it just above this upper ligature To the other end of the eel skin was fixed a bladder and wooden pipe, similar to what is used in giving a clyster, only the pipe was large enough to let the end of the probang pass into the bladder without filling up the passage The probang thus covered was introduced into the stomach, and the food and medicines were put into the bladder and squeezed down through the eel skin "

On the basis of the above evidence I think we must credit John Hunter with the first recorded use of a stomach tube, but in 1797 Alexander Munro III delivered as his graduation dissertation at the University of Edinburgh a paper entitled "De Dysphagia " In this paper he questioned the priority of Hunter and stated that in 1767 his father had used a flexible tube of coiled wire covered with leather to remove dangerously fermenting fluids and gases from the stomachs of cattle

Baron Larrey, Napoleon Bonaparte's Surgeon-General, recounts in his

"Memoirs" the use of stomach or esophageal tubes to feed patients with tetanus and how in the case of Marshall Murat such tubes had to be used to feed him because of a severe wound in his neck. It is very doubtful, however, if he ever passed the tubes into the stomach for he states that the position of the tube was determined before feeding by injecting a few drops of water to see if the patient coughed.

Dupuytren and Renault in Paris had followed up Boerhave's suggestion that a flexible stomach tube would be a practical and useful instrument and by 1803 had perfected an instrument and published a description of it. I have been unable to find evidence that they ever used the instrument except on experimental animals.

EARLY APPLICATION OF STOMACH TUBES FOR THE REMOVAL OF POISONS

Philip Syng Physick, a Philadelphia surgeon, knowing nothing of the preceding work, began to advocate washing out the stomach with a tube and syringe in cases of poisoning in 1800. Such recommendations appeared in his lectures to the students at the University of Pennsylvania and his nephew, Dr Dorsey, had special tubes constructed for that purpose in Paris in 1803. Dorsey tried the procedure in 1809 but was unsuccessful in saving his patient. The first article on the subject by Physick appeared in *The Eclectic Repository and Analytical Review*, Vol 3, 1813. He related how on June 6, 1812, he was called to visit twins, three months old, who, having whooping cough, were each given one drop of laudanum by their mother to ensure a good night's sleep. The cork had been left out of the laudanum bottle for some time and evaporation had increased the strength of the tincture so much that both babies became comatose with morphine poisoning. Physick, feeling sure they would die, used a urethral catheter and syringe to wash out the stomachs of both infants. One died, but the other completely recovered.

This is the first authentic record we have of a tube being used to remove noxious or poisonous substances from the human stomach. It will be remembered that Hunter used the tube only to convey medicines and food into the stomach.

On May 29, 1822 Mr Jukes, an English surgeon of Westminster, published in an obscure periodical, the *Gazette of Health*, a description of what he called "a stomach pump." It was made of a two-foot rubber tube one-quarter inch in diameter. The distal end had several perforations and an ivory bead at the tip. To the proximal end was attached an elastic bottle also made of rubber. Jukes advocated the use of this instrument in cases of poisoning to empty and wash out the stomach. He had experimented on dogs and himself to prove its effectiveness. In fact on one occasion he took 10 ounces of laudanum into his stomach and evacuated it without harm to himself. In the fall of 1822 two papers were published in the *London Medical and Physical Journal*. One in September was by a Mr Bush of Frome, the other in November by Mr Jukes.

These papers described an instrument to be used for washing out the stomach in cases of poisoning. Both instruments were rubber tubes of similar make, but in place of the elastic bottle used by Jukes, Bush advocated the use of a syringe. Jukes immediately claimed priority on basis of his earlier publication in the *Gazette of Health*. Sir Astley Cooper became interested in what everyone in England considered to be a new invention. At his lecture at St. Thomas Hospital, Wednesday, December 10, 1823 he had Jukes appear and demonstrate his new instrument. The tube employed was connected with a special syringe made by Mr. Reed of Kent. This was considered a great improvement over the original instrument made by Jukes in 1822 because of the special construction of two valves which eliminated the necessity of removing the syringe from the tube.

With this lecture Garrison says the procedure of gastric lavage in cases of poisoning became definitely established in English medical practice. Thus we see that by 1823 the stomach tube had been "invented" in France, England and the United States and, as far as can be determined, without knowledge of what had occurred in the other countries.

It is hard to understand how such a useful and at times life saving procedure as gastric lavage once having come into use could be so neglected and forgotten as seems to have been the case at the middle of the nineteenth century. The only improvement in the construction of stomach tubes or in their use from the time of Jukes' publications in 1823 to Kussmaul's classic paper in 1869 was the suggestion of Arnott in 1829 and Somervail in 1832 that siphonage be used in gastric lavage instead of forceful suction.

MODERN DEVELOPMENT IN THE CONSTRUCTION AND USE OF THE STOMACH TUBE

To Kussmaul we must give credit for reviving a clinical interest in the stomach tube. Through contact with Bowditch of Boston he was acquainted with a model of the stomach tube and pump constructed by Dr. Wyman, also of Boston. Bowditch had used this to aspirate empyema cavities. He gave Kussmaul the specifications and the latter had the instrument maker, Fischer of Freiburg, make such a pump. On July 22, 1867, Kussmaul made a diagnosis of gastric dilatation due to pyloric ulcer on a peasant girl of 25 named Marie Weiner. Using the "American pump" he treated this patient by frequently emptying and lavaging her stomach. The patient recovered. By 1869 he had treated 12 similar cases and wrote his famous paper entitled "Über die Behandlung der Magenerweiterung durch eine neue Methode mittelst der Magenpump". This paper received a wide circulation and had a profound influence on the treatment of gastric disease throughout Europe and America. B. B. V. Lyon says that this paper was directly responsible for Billroth's interest in gastric surgery. Possibilities for the diagnosis and treatment of gastric diseases were seen immediately and the improvements in the instruments by which they could be made soon began to appear.

Theodore Jurgensen in 1870 reminded the profession again of the possible dangers of forceful suction during gastric lavage and emphasized the practicability and simplicity of siphonage. Auerbach and Ploss independently developed double recurrent stomach tubes in 1870. Their tubes had the disadvantage of being large and causing the patient considerable discomfort when used, but gastric lavage could be done more thoroughly and more rapidly.

In 1871 Leube saw clearly the diagnostic possibilities for studying gastric physiology by using the stomach tube. It was he who first suggested the test meal. In 1874 Ewald and Oser developed stomach tubes of soft pliable rubber and of smaller caliber than had been used heretofore. Up to this time stomach tubes, while flexible after a fashion, were stiff and hard and entailed in their passage a considerable unavoidable discomfort to the patient. It was considered necessary to employ a stiff tube because of the force which was used in its passage. No cooperation was expected from the patient. A few soft pliable tubes had been used but were always inserted with a stylet or mandarin. Ewald and Oser first showed that soft rubber tubes could easily be passed without stylets if the cooperation of the patient could be secured. How much this meant to the patient in the way of increased comfort can easily be imagined.

Our tubes of today are practically the same as those used by Ewald and Oser. The quality of the rubber is better but the principles of construction and the technic of insertion and use are the same. Suggested improvements have not ceased to appear but with one or two exceptions have not been accepted by the profession as practical or worthwhile. Marcy in 1883 emphasized that in double recurrent tubes the efferent tube must always be larger than the afferent one. The last important change in the construction of the stomach tube was made by Rehfuess in 1914. This tube was in fact merely a variation of Einhorn's duodenal tube used to obtain samples of gastric contents for examination. It is not suitable for therapeutic purposes and has in no way replaced the larger caliber tubes for lavage.

EARLY ATTEMPTS AT DUODENAL INTUBATION

The impetus which medical thought received from Kussmaul's paper can scarcely be overemphasized. Throughout the world investigators set about to study the physiology and pathology of the stomach, and it is not strange that soon experimentation began in an effort to make the duodenum and its secretions available for examination and analysis. The duodenal tube in contrast to the stomach tube was entirely an American development and a direct result of this desire to reach the duodenum for diagnostic purposes. Before the invention of the duodenal tube in America, Boas and Boldyreff in Europe tried to obtain duodenal secretion, Boas, by massaging the right upper quadrant of the abdomen, tried to cause a reflux of fluid through the pylorus, and Boldyreff, by giving fatty meals, tried to obtain the same results as an effect of normal physiology. That they succeeded

in some cases is undoubtedly true but neither method was practical or reliable

The American, Fenton B Turck, presented to the International Medical Congress at Rome in 1894, a curious and complicated instrument which he called the "gyromele" This was a revolving flexible steel cable tipped with a spiral spring and sponge This cable was encased in a rubber tube and at the proximal end fitted with a drill arrangement to enable it to be rapidly rotated Originally designed to outline the stomach by palpation through the abdominal wall, this instrument went through many modifications and with it Turck claimed to have intubated the duodenum and obtained duodenal secretions, although few men other than himself ever used it

J C Hemmeter²³ of Baltimore in 1896 reported certain experiments he had carried out in an attempt to intubate the duodenum He first passed a balloon into the stomach This was roughly in the shape of the stomach with a groove running along the lesser curvature Through this groove a rubber tube was passed into the duodenum To prove that the tube actually entered the duodenum, Hemmeter took roentgen-rays of the tube in place But this again was an impractical and cumbersome procedure and created but little interest until brought into controversy 14 years later after Einhorn and Gross presented their simple duodenal tubes

The German, F Kuhn, had worked with Hemmeter at Baltimore in 1895-1896 and had assisted him with the experiments mentioned above With a rubber covered steel spiral he tried to catheterize the pylorus directly After returning to Germany he developed the method further and wrote a description of it in 1898 In general, this method was not considered reliable or practical and never received the attention which its inventor thought it deserved, but it is no doubt true that Kuhn frequently was able to reach the duodenum with his spiral tube

THE INVENTION AND DEVELOPMENT OF THE MODERN DUODENAL TUBE

In 1909, almost simultaneously Maurice Gross⁹ and Max Einhorn¹⁴ presented to the medical profession a simple method of obtaining duodenal secretions Einhorn proposed a small metal olive or capsule perforated and attached to a long thin rubber tube The capsule was to be swallowed in the evening and the peristalsis of the stomach allowed to carry the tube into the duodenum Aspiration of fluid was to be done with a syringe Gross also proposed a tube with a perforated metal capsule This tip was more than twice as heavy as Einhorn's and he depended upon gravity as well as gastric peristalsis to carry the tube to the pylorus and into the duodenum To accomplish this he recommended that the patient lie on his right side after the tube had been swallowed

As Kussmaul in 1869 had begun a new era in the study of gastric disease, so Einhorn and Gross initiated another period of experimentation and study of gastrointestinal pathology Internists were the first fully to grasp the significance of the opportunities afforded by this simple new instrument Its use quickly spread to Europe, and literally dozens of men began to use

it extensively. The literature on the subject after 1910 is voluminous. Each one who used the duodenal tube seems to have thought that he could improve on its construction or on the technic of its use. As a result, between 40 and 50 different duodenal tubes are described in the German, French, and English literature. The majority of them, however, are but variations of the original tubes and most of them employ the principle of a weighted tip and narrow soft rubber tube. The work of Hess and the tube of Levin deserve special mention. In 1912 the New York pediatrician, Alfred Hess, described the use of a small Nelaton catheter for duodenal intubation in infants. Due to the anatomical relationships of the infant stomach this procedure could easily be carried out. A. L. Levin of New Orleans in 1921 described his smooth catheter tipped duodenal tube for adults. This tube has the advantage over most other duodenal tubes because it may be passed through the nares and is made of one solid piece of rubber. The tube has found increasing favor since its introduction.

Speed of intubation has been a goal of all who have used duodenal tubes and has been one of the reasons for the multiplicity of types developed. As stated above, Emhorn passed the tube in the evening and allowed 10 to 12 hours for peristalsis to carry it into the duodenum. Gross claimed that intubation could be done much more rapidly with his tube using gravity as an aid to gastric peristalsis, one to two hours being the average time required. Lippman made a scientific study in 1914 of the technics used in passing duodenal tubes and developed his own technic based on this study. His method is briefly described as follows. The patient is placed in a chair and the freshly oiled tube passed into his fasting stomach for a distance of 45 centimeters. After bending slightly forward for a minute, the patient partially reclines lying on his right side and the tube is slowly inserted 25 centimeters farther. This position is maintained for five minutes and then the patient turns on his back and fully reclines while his hips are elevated slightly. Five minutes later the tube is inserted 10 centimeters farther. This should place the tip of the duodenal tube in the duodenum. It is claimed that with this technic, duodenal tubes can be passed in normal persons in 15 to 30 minutes.

Many tests have been suggested and used to localize the tip of the duodenal tube. All writers agree that the only positive way is by either the fluoroscope or an x-ray plate, but fairly reliable tests include the gross appearance and reaction of the aspirated fluid and the milk or colored fluid test.

THE CLINICAL APPLICATION OF THE DUODENAL TUBE

The more important uses to which duodenal tubes have been put will be briefly summarized with emphasis on one or two of these uses. The examination and analysis of duodenal secretions is the prime purpose for which the duodenal tube was invented and continued to be its most important use up to about 10 years ago. The past decade, however, has seen an ever-widening use of the tube as a therapeutic agent in the treatment of both

medical and surgical conditions At the present time, moreover, by far the greater part of the publications concerning this instrument deal with its use in the treatment of gastric and intestinal distention rather than in diagnosis

Gross,²⁰ Schmidt, and Jutte have all recommended duodenal lavage and duodenal insufflation of oxygen for a number of conditions, the most important being auto-intoxication and intestinal catarrh Lyon⁴⁰ has been preeminently interested in the non-surgical drainage of the gall-bladder with magnesium sulphate instilled through the duodenal tube Gantt and Weist, Simon, and Gunn have used it in the treatment of intestinal parasites Carnot and Libert, Lihenthal, and McDonald have found it useful for feeding in cases of dysphagia, anorexia and persistent vomiting Soper recommends it in the treatment of hematemesis Young has used it for feeding in uremia Dudko and Brailowski by inflating the duodenum with air were able to cause a nail lodged there for two weeks to pass A number of writers have described its use in the treatment of peptic ulcer The more important of these are Einhorn and Buckstein

While surgeons have only of late years used the duodenal tube extensively for any purpose other than diagnosis, Westermann, as early as 1910, reported 15 cases of severe peritonitis with gastrointestinal stasis treated by continuous siphonage drainage of the stomach by means of a small tube passed through the nose but remarked that the siphonage was interrupted from time to time by gas A year later Kappis reported 10 similar cases treated in the same way and warmly recommended that method of treatment Kanavel, in 1916, recommended that closed systems be applied in the use of such tubes Willy Meyer used duodenal tubes, after gastric operations, for aspiration and administration of fluids The general use of siphonage drainage of the stomach in postoperative treatment and in any condition accompanied by gastric and intestinal paresis was earnestly advocated by Matas in 1924 Since that time practically every treatise on postoperative treatment includes the use of the duodenal tube for siphonage drainage post-operatively in cases of persistent vomiting or distention

The application of continuous suction to duodenal tubes originated with Ward of San Francisco A description of his apparatus appeared in 1925⁶¹ In 1929 he described his suction method of treatment in cases of acute general peritonitis⁶⁵ and in 1930⁶⁶ the application of the same method to the treatment of acute dilatation of the stomach Stout in 1931 mentions the use of the duodenal tube as an adjunct to operative procedures in the treatment of intestinal obstruction His main purpose in using the tube was to drain the stomach and thereby improve the patient as a surgical risk One receives the impression after communicating with surgeons of wide experience that use of the duodenal tube as a siphon postoperatively and in certain other conditions had become fairly common by 1930, but few men had realized the increased efficiency which occurred with the application of suction to such tubes In 1931 Wangensteen of Minneapolis was the first to utilize the principle of continuous suction transmitted through a duodenal tube as

an effective means in the treatment of certain cases of mechanical obstruction^{60, 61, 62} He had observed that, following the establishment of enterostomy in mechanical obstructions of the small intestine of adhesive origin, drainage was often minimal after decompression had been effected This occurrence suggested the possibility of draining the gut by duodenal intubation alone, rendering operation frequently unnecessary In a large number of instances of adhesive obstruction, decompression by suction applied to a duodenal tube has proved effectual⁶³

Paine and Wangenstein in 1933 showed that duodenal tubes draining the upper gastrointestinal tract were much less efficient when allowed to act as siphons than when constant suction was maintained These same writers have also shown the excellent prophylaxis which suction affords against distention of the gastrointestinal tract, provided it be instituted before the distention has progressed to an extreme degree⁴⁸ Attempts to decompress a markedly distended parietic gastrointestinal tract are much more apt to be unsuccessful than in cases where an active peristalsis is still present

SUMMARY

The origin of the stomach tube can be traced as far back as the time of the Roman Emperor, Claudius, who lived at about the time of the birth of Christ The first stomach tube was probably made and used by John Hunter in the latter part of the eighteenth century Almost simultaneously and as far as can be determined independently, improved stomach tubes were invented in the United States, France, and England between 1800 and 1822 By 1865, when Kussmaul rediscovered it, the stomach tube had been practically forgotten Within a few years, however, improvements in its construction and the technic of its use again established the stomach tube as an indispensable therapeutic and diagnostic agent

The invention of the duodenal tube is entirely an American development, Turck and Hemmeter doing the pioneer work in the last decade of the nineteenth century, and Einhorn and Gross simultaneously in 1909 presenting to the medical profession simple practical duodenal tubes Many modifications of the duodenal tube have appeared since, but no radical changes have been made in its construction The past 10 years have seen, however, a notable change in its use

At the present time, while the duodenal tube is still extensively used as a diagnostic instrument, its use in the treatment of disease is being more and more emphasized Surgeons, who have been the last to avail themselves of the advantages which this instrument affords, are now making the greatest progress in its use

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EDITORIAL

ASCORBIC ACID

A KNOWN chemical substance, hexuronic acid, has justifiably been re-named ascorbic acid to indicate its identity with the antiscorbutic vitamin C.

This simple statement should quicken the pulse of anyone familiar with the long story of scurvy, the slowly won knowledge of the vitamins, and the marvelous achievements of chemistry in biological fields not so long ago wholly closed to us. That the significance of this name giving has been appreciated by laymen is evidenced by an editorial in the *New York Times* for Sunday, September 9, 1934. To us physicians the event should bring an even greater satisfaction.

It may not mean much to many of us that the chemical formula of ascorbic acid is $C_6H_8O_6$ or that it is the enolic form of 3-keto-l-gulo-furano-lactone with an extraordinarily flat molecule as shown by the x-ray data. It is important, however, that a substance which can be crystallized out from natural sources and can be synthesized from xylosone is apparently identical with a vitamin. How short a time ago it was when we talked of "accessory food substances" and knew little or nothing of what we spoke! Not that scurvy was not known nor the curative value of lemons recognized for hundreds of years but the nature of the active agent could not even be surmised.

Properly to appreciate what has been accomplished in the prevention of scurvy one should read one or another of the excellent historical descriptions of the disease—preferably that by Karl Vogel¹—Scurvy—"The Plague of the Sea and the Spoyle of Mariners" or that in Major's² "Classic Description of Disease". One who does, will soon realize the truth, however, of Oliver Wendell Holmes' remark that medicine had "learned from a sailor how to keep off scurvy."

No better account of the specific effect of an antiscorbutic was ever written than that in the fifteenth chapter of the 1600 edition of "The Principal Navigations" by Hakluyt. It describes the experiences of Jacques Cartier on the voyage on which he discovered and explored the Saint Lawrence River. It reads:

"Our Captaine considering our estate (and how that sickness was encreased and hot amongst us) one day went forth of the Forte, and walking upon the yce, hee saw a troupe of those Countreymen comming from Stadacona, among which was Domagaia, who not passing ten or twelve days afore, had been very sicke with that disease, and had his knees swolne as bigge as a childe of two yeres old, all his sinews shrunke together, his teeth spoyled, his gummes rotten, and stinking. Our Captaine seeing him

¹ Bulletin New York Academy of Medicine, 1933, 1, 459

² Major, R. H. Classic description of disease, 1932, C. C. Thomas, Baltimore

whole and sound, was thereat marvellous glad, hoping to understand and know of him how he had healed himselfe, to the end he might ease and help his men. So soone as they were come neere him, he asked Domagaia how he had done to heale himselfe. he answered, that he had taken the juice and sappe of the leaves of a certain Tree, and therewith had healed himselfe. For it is a singular remedy against that disease."

From this empiric use of what was probably the sassafras tree to our present knowledge of the distribution of ascorbic acid is a long stride. For since the identity of this substance has been established and a chemical test for its recognition developed, it has become possible to test materials directly for its presence, and it has been found in high concentration in some unexpected places. For example, ascorbic acid is present in the adrenal cortex in three times its concentration in the lemon. This does not mean that the adrenal is a mere storage depot, for ascorbic acid may play a part in the normal functional activities of the organ. Certainly, however, the content drops as scurvy appears. Ascorbic acid has also been found in certain other tissues, in some tumors, and in many plants. A high concentration has been "discovered" in paprika and this is a new and valuable source of this material although in 1598 it was written of the scurvy that "Beere or white wine or Syder boiled with Graynes and Long Pepper is very singular good."

The naming of ascorbic acid marks an important step but not the final one in our study of scurvy, we have yet to learn why a lack of vitamin C causes this well known disease picture. How does the absence of anti-scorbutic material lead to spongy gums, to hemorrhagic phenomena, to anemia, to cardiac weakness and death? Now that the pure material is available an answer to these questions may be found—already it is known that ascorbic acid is a promoter of respiratory systems in the tissues, and it is to be expected that a lack of ascorbic acid in the tissues will result in a diminished oxidative activity.

The quantity of research which has and continues to be centered on the vitamins is enormous. In the excellent summary given in this year's "Annual Review of Biochemistry" by L. J. Harris there are references to 77 articles on vitamin C alone.

Possibly by means of these researches on scurvy fundamental processes will be explained of wide application. Whether this occurs or not, the results already obtained justify the enormous effort, the countless publications, the animal experiments which have been expended in the study of scurvy. The unreachable horizon of complete knowledge is never reached—but it is important that we should appreciate and glory in the progress made. That science has approved the name ascorbic acid is evidence of such progress.

O. H. PERRY PEPPER

REVIEWS

The Spastic Child By MARGUERITE K. FISCHEL 97 pages, 13 x 20 cm C V
Mosby Company, St. Louis 1934 Price, \$1.50

The "spastic child" has always been a problem of such severe nature and complex character that few physicians will interest themselves sufficiently to really study the case and intelligently help the parents to rehabilitate the patient. It has fallen to the lot of the orthopedist and physical therapist to do most of the work, but that is not enough. It takes the care, the infinite patience, the stable character and the love of a mother to really develop the majority of these patients into a worthwhile, economic asset.

The author of the above book rightly and justly criticizes the medical profession for its lack of sympathetic understanding of the parents and the child, though medical knowledge is meager, even almost minus, relative to the ramifications of Little's disease.

Much can be done for these patients provided physical and mental education is instituted early and intelligently, and is carried out consistently and steadily for years. Mrs. Fischel has shown the value of such a regime in the face of other difficulties which might have deterred one of less courage. Her book is short, clear, accurate, and encouraging to parents and physicians. It is an excellent book to be used as a guide by all who deal with "spastics." The illustrations and directions are simple and sufficient, and the result proves the efficiency of the basic principles, provided they are followed consistently and persistently.

Mrs. Fischel is to be congratulated upon her result and deserves thanks for her presentation of her methods. The reviewer expects to refer all mothers of spastic children to this book for instruction and guidance.

A. V.

Essentials of Infant Feeding and Paediatric Practice By HENRY P. WRIGHT
212 pages, 14.5 x 22.5 cm Oxford University Press, London 1934 Price,
\$4.25

This small book attempts to present its large subject in a condensed form, thereby, as the author states, "to help the student of medicine in a crowded curriculum and the general practitioner in a strenuous life."

There are three main sections. The first deals with the growth and development, the physiology, and the care and feeding of the infant. All topics are treated briefly. The use of zinc stearate is advocated without warning of the danger of an inhalation pneumonia. It does not seem to be in accord with the modern pediatric trend to use "force-feedings" in refractory infants when different foods are added to the diet. The chapter on "Artificial Feeding" is in concord with the general tenor of briefness and contains a presentation of the author's method plus a discussion of lactic acid feeding. In this part, as well as in subsequent sections, the author has drawn rather heavily on numerous authorities, whom he mentions in the preface.

The second section is devoted to nutritional disturbances and vitamin deficiency diseases. The author heads each chapter on Failure to Gain, Vomiting, Diarrhea and Constipation, with an outline form of the causes placed under the headings of Constitutional, Infection, Food, Environment and their appropriate subdivisions. Such a method of dealing with these problems may well serve to render a great number of medical men dealing with infants less "food-conscious." Included in this section is also a chapter on Prematurity and Acidosis, the latter being mostly drawn from Marriott's "Infant Nutrition."

The third part is a miscellaneous grouping of therapeutics, laboratory data, history forms and diet lists. In the article on intravenous therapy, the author presents only one method of entering the vein, namely by dissection. Needless to say, this is not always necessary.

The basic idea of the book is to be commended. There are, however, in its pages many recommendations which do not seem in accord with accepted pediatric practice, and in his dependence on the literature the author seems to have somewhat submerged his own individuality.

E B

The Power to Love By EDWIN W. HIRSCH, M.D., Associate in Urology, College of Medicine, University of Illinois. 363 pages. Alfred A. Knopf, New York. 1934. Price, \$4.00.

This book discusses the psychic and physiologic factors in "regeneration" and there is no doubt that although many books on the subject of sex have come off the press since the postal authorities let down the bars on such literature, this is one of the frankest books. As the publishers state, it is written primarily for men, but undoubtedly it will also be read by women. It will be criticized, but this book has a definite purpose to serve and it will be frequently referred to by physicians.

The author states that "Careful surveys made among groups of men reveal the fact that, no matter what the intellectual equipment of men may be or what position they occupy in society, a large proportion are unable to exert their sexual proclivities in a satisfactory manner." The author then goes on in 10 chapters to explain the sexual regulatory mechanism, causes of sexual debility, medical and surgical treatment of impotency, psychical impotence, frigidity and its relation to impotency, premature ejaculation, sexual fear, the art of sexual technique, systems of sexual control, and the power to love. It is the reviewer's opinion that every physician should read this book, but it is also his opinion that this book should be considered a textbook for the profession and not something for popular sale.

It is evident that the author considers himself as writing for the profession as he says "One must have the qualifications and acumen of the internist, the comprehensive knowledge of the neurologist, the searching eye of the venereologist, the wisdom of the sexologist, and the tact of a diplomat. If physicians would unravel the mystery of sex, they must study the secrets as taught by the psychoanalytic and psychotherapeutic schools of practical sexology."

Hirsch shows an excellent insight into psychotherapy, and although he does not claim to be a psychiatrist, it is evident that he feels that this step-child of medicine has contributed much to scientific medicine and is here to stay. In the field of sexology it is of greatest importance.

J. L. McC

Practical Talks on Heart Disease By GEORGE L. CARLISLE. 153 pages, 14.5 × 22.5 cm. Charles C. Thomas, Baltimore. 1934. Price, \$2.00.

This small volume presents in a forceful style the author's personal opinions in regard to various types of cardiovascular disease and their treatment. The reviewer feels that the material as presented fails to make it easy for the general man to diagnose and treat properly 90 per cent of abnormal hearts, which state of affairs should exist according to the author's preface. The chapter on Syphilitic Heart Disease, and the discussions of Irregularities of the Heart and of Heart Pain are especially inadequate both as regards diagnosis and treatment.

W. S. L., Jr.

Medicine Marches On By EDWARD PODOLSKY 343 pages, 15 × 22.5 cm Harper and Brothers, New York 1934 Price, \$3.50

Dr Podolsky has produced a book written in sprightly journalese dealing with the advance of medicine. He has written it with an eye to the historical aspect as well as the present status of medicine and has included many of the more important things which have been done in medicine and surgery both in recent years and in the past. He has also included some newer discoveries which most of us would consider still in the observational stage and his positive statements about them make modern medicine seem a little more remarkable than it really is and lend an air of romance to the book.

J R

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Dr Russell L Cecil (Fellow), New York, N Y, has donated an autographed copy of his "Text-Book of Medicine" to the College Library of publications by members This is the third edition, revised and reprinted during 1934 Forty-one Fellows of the College are contributors

Acknowledgment is also made of the following publications

Dr Arnold S Anderson (Fellow), St Petersburg, Fla —1 reprint

Dr J C Kamp (Fellow), Casper, Wyo —1 reprint

Dr Maxim Pollak (Associate), Peoria, Ill —1 reprint

Dr Irving W Schiller (Associate), Boston, Mass —1 reprint

Dr John W Shuman (Fellow), Los Angeles, Calif —1 reprint

Dr S A Slater (Fellow), Worthington, Minn —1 reprint

Dr George R Minot and Dr William P Murphy, of Harvard University Medical School, and Dr George H Whipple, of the University of Rochester, have been named winners of the Nobel Prize in medicine for 1934 This year the prize totals \$41,000, and was awarded to the three physicians "for liver therapy in anemia"

Dr Minot is an active Fellow of the American College of Physicians Dr Whipple was formerly a Fellow of the College

Dr Walter L Bierring (Fellow), Des Moines, Dr James D Bruce (Fellow), Ann Arbor, Dr James Alex Miller (Fellow), New York City, Dr George Morris Piersol (Fellow), Philadelphia, and Dr Stewart R Roberts (Fellow), Atlanta, were among those appointed by Secretary Perkins, Chairman of President Roosevelt's Committee on Economic Security, as members of the Medical Advisory Board "to advise the committee's technical staff in its study of programs of public health, medical care and health insurance" The Board met at Washington, November 14 and 15 Owing to the fact that the Medical Advisory Board will make its recommendations to the Committee on Economic Security, no report of its deliberations has been given, but it is understood that the technical staff of the Committee presented to the Board tentative proposals on extending and improving public services, tax supported medical care for dependents and other population groups affected with certain diseases, and health insurance against illness

Dr David Riesman (Fellow), Philadelphia, was selected as President-Elect of the International Postgraduate Medical Assembly of North America at its annual meeting in Philadelphia, November 5 to 9

The First International Congress of Gastro-Enterology will be held at Brussels, August 8 to 10, 1935, under the presidency of Dr J Shoemaker of The Hague, Holland, and under the patronage of Their Majesties, the King and Queen of Belgium The Secretary-General of the Congress is Dr George Brohee, rue de la Concorde, 64, Brussels, Belgium

Dr Max Einhorn (Fellow), of New York City, has been asked to form and act as Chairman of the North American Committee and Dr DeWitt Stetten has accepted the post of Secretary

Dr Louise Tayler-Jones (Fellow), of McLean, Virginia, was reelected Vice-President of the International Association of Medical Women at the Third Quinquennial Congress, meeting in Stockholm, August 8 to 12, 1934 Dr Tayler-Jones is the only officer from the United States About three hundred medical women attended the different sessions of the Congress, which is composed of members from 29 different countries

Dr Elizabeth Bass (Fellow), of New Orleans, Louisiana, attended the Congress of the International Association of Medical Women as a delegate from the United States Following the Congress, Dr Bass spent several days in Soviet Russia

Dr Joseph B Wolffe (Associate), Philadelphia, was honored by a testimonial dinner recently by the Physicians Square Club of America, Philadelphia Chapter, marking Dr Wolffe's recovery of the vision of one eye, which had temporarily been lost due to an accident which occurred while he was conducting experimental research work several months ago Dr Wolffe is Associate Professor of Medicine and Cardiologist at Temple University Medical School

Dr R H Kuhns (Associate), formerly Director of Research at the Illinois State Psychopathic Institute, has been appointed Instructor in Neuropsychiatry at the University of Illinois College of Medicine

Dr Maurice Lewison (Fellow) is the President of the newly organized Hebrew University Society of Chicago, the purpose of which is to support the Hebrew University in Palestine, particularly the proposed University Hospital and medical center which is being built on Mount Scopus in Jerusalem This society is affiliated with the American Jewish Physicians Committee of New York, of which Dr Nathan Ratnoff is President, and Dr Emanuel Libman (Fellow) is Chairman of the Executive Committee

Dr Percy M Ashburn (Fellow), Washington, D C, Colonel, U S Army (Retired), has become Superintendent of Columbia Hospital for Women, Washington, D C

Dr Ralph R Hendershott (Associate), Tiffin, Ohio, has been chosen President-Elect of the Ohio State Medical Association

Dr Arthur C Christie (Fellow), Washington, D C, was elected President of the International Congress of Radiology at their meeting in Zurich, Switzerland The next Congress of this organization will be held in the United States in 1937 Dr Benjamin H Orndoff (Fellow), Chicago, has been elected General Secretary

Dr L J Moorman (Fellow), Oklahoma City, is now President of the Southern Tuberculosis Conference

Dr Roscoe L Sensenich (Fellow), South Bend, Ind, has been selected President-Elect of the Indiana State Medical Association for 1934 to 1935

Dr Francis H Smith (Fellow), Abingdon, Va, was recently installed as President of the Medical Society of Virginia for 1934 to 1935

Dr Alexander F Robertson, Jr (Fellow), Staunton, Va, was elected a Vice-President of the Society at its last annual meeting

Dr Oscar M Gilbert (Fellow), has resigned as Associate Professor of Medicine at the University of Colorado School of Medicine, and has been made Emeritus Professor of Medicine. He has been connected with the School since 1900

Dr Thomas D Cunningham (Associate) has resigned as Assistant Professor of Medicine at the same institution

Dr Sylvester D Craig (Fellow), Winston-Salem, N C, has been made President of the State Board of Health

Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, was elected President of the Central Society for Clinical Research at its recent annual meeting

Dr D O N Lindberg (Fellow), Medical Director and Superintendent of the Macon County Tuberculosis Sanatorium, Decatur, Ill, has been reelected Secretary-Treasurer of the Mississippi Valley Sanatorium Association

Dr Joseph L Miller (Fellow), Chicago, delivered the Presidential Address at the Nineteenth Annual Meeting of the Institute of Medicine at Chicago, November 4, his subject being "The Influence of Claude Bernard's Experimental Methods on Medicine"

Dr Hilton S Read (Fellow), Atlantic City, N J, has been appointed Chairman of the Committee on Arrangements for the annual meeting of the Association for the Study of Internal Secretions which will be held at Haddon Hall, Atlantic City, June 10 to 11

Dr Gerald B Webb (Fellow and Governor), Colorado Springs, delivered the first John W Bell Lecture before the Hennepin County Tuberculosis Association, Minneapolis, on December 3. Dr Webb was formerly President of the National Tuberculosis Association, now President of the Colorado State Board of Medical Examiners and is an ex-President of the Colorado State Medical Society

Dr Walter Freeman (Fellow), Washington, D C, was elected Secretary of the newly organized American Board of Psychiatry and Neurology

Dr Ross V Patterson (Fellow), Philadelphia, was reelected President of the Association of American Medical Colleges at the annual meeting of that organization in Nashville the latter part of October

Dr Thurman D Kitchin (Fellow), Wake Forest, N C, is Vice-President

Dr George W Parson (Associate), Texarkana, Tex, has been elected Secretary of the Tri-State Medical Society (Arkansas, Louisiana, Texas)

OBITUARIES

BAILEY KELLY ASHFORD

Dr Bailey Kelly Ashford, Colonel, U S Army (Retired), and Professor of Tropical Medicine and Mycology, University of Puerto Rico School of Tropical Medicine (*affiliated with Columbia University, New York City*), died November 1, 1934, at his home in San Juan, Puerto Rico.

Dr Ashford was born September 18, 1873, in Washington, D C. His undergraduate work was done at Columbian University, now the George Washington University. He received his degree of Doctor of Medicine in 1896 from the Georgetown University Medical School and honorary degree of Doctor of Science from the same Institution in 1911. His internship was at the Children's Hospital, Washington, D C, 1895-1896, and at the Home for Incurables, Washington, 1897. Dr Ashford entered the Medical Corps of the U S Army, 1897, and rose to the rank of Colonel. In 1898 he went to Puerto Rico as a member of the military expedition, remaining throughout the occupation of the island by the United States, and was in command of medical department troops. In 1899 he recognized ancylostomiasis as the cause of the anemia prevalent among the rural population of Puerto Rico, and, later on, in 1904, founded the Puerto Rico Anemia Commission to carry on a campaign to combat that disease. He also conducted an extensive research on the etiology and treatment of sprue. He assisted in creating the Institute of Tropical Medicine in 1911, which led to the establishment in 1924 of the School of Tropical Medicine of the University of Puerto Rico, *in affiliation with Columbia University, in which School* Colonel Ashford continued as Professor of Tropical Medicine. In 1933 he received honorary degrees from both Universities. During this same year the Government of Puerto Rico placed the Ashford bust in the School as a memorial.

During the World War Colonel Ashford accompanied the First Division to France as medical officer, and he later trained the medical personnel at the front. The United States Congress conferred on him the Distinguished Service Medal, and England conferred on him the Cross of St George and St Michael for services with the British.

He was a member of the American Society of Tropical Medicine, the Royal Society of Tropical Medicine (England), the American Association of Military Surgeons, the Academy of Medicine of Puerto Rico, the Puerto Rico Medical Association, the American Society for Clinical Investigation, and the Association of American Physicians. He was a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, and a Fellow of the American College of Physicians, having been elected during 1923. Colonel Ashford held many positions of honor among

his societies, including the Presidency of the American Society for Tropical Medicine, the Vice-Presidency and the Presidency of the Puerto Rico Medical Association. He was the author of numerous articles in various leading medical journals and the editor of "Medical History of the World War." He was a delegate in 1910 from the United States to the International Conference on Industrial and Alimentary Hygiene in Brussels, in 1916 he was appointed by the Rockefeller Foundation a member of the Medical Commission to Brazil, and in 1928 he was a delegate to the International Congress of Tropical Medicine and Hygiene at Cairo, Egypt.

In recognition of his outstanding contributions to, and his enthusiastic work for the American College of Physicians, Colonel Ashford was elected Governor of the College for Puerto Rico and surrounding territory in 1934.

THOMAS EDWARD SATTERTHWAITE

Dr Thomas Edward Satterthwaite, probably the oldest Fellow of the American College of Physicians, died September 19, 1934, aged 91 years.

Born in New York in 1843, he attended Yale University from which he received his A B degree in 1864, and then attended Columbia University College of Physicians and Surgeons from which he received his medical degree in 1867. He served his internship in the New York Hospital and then went abroad for study in Vienna. While abroad, the Franco-Prussian War started and the young Dr Satterthwaite entered the Prussian Army as a surgeon. On his return to the United States in 1872, he became affiliated with the St Luke's Hospital, of New York City, working first as a microscopist and then as a pathologist. He became a specialist in pathology and diseases of the heart, and from 1873 to 1888, he was the pathologist to the Presbyterian Hospital. He was one of the founders, one time secretary, vice-president and professor of pathologic anatomy and general medicine, at the New York Post-Graduate Medical School. In 1875, he organized the medical and surgical staff of the Chambers Street House of Relief, now the Hudson Street Hospital. He was the founder of the Babies' Hospital in 1894, and was its president until 1899. During the later years of his practice, he was consulting physician to the Post-Graduate, Orthopedic and Manhattan State Hospitals. He held the rank of first lieutenant in the U S Army Reserve Corps from 1911 to 1917.

Dr Satterthwaite was the author of many articles appearing in leading medical journals, and of the "Manual of Histology," "Practical Bacteriology," "Disease of the Heart and Aorta" and "Cardio-Vascular Diseases." He was a member of the Medical Society of the State of New York, Society of Medical Jurisprudence, American Medical Association, New York Academy of Medicine, Association of Military Surgeons of the United States and the Harvey Society of New York. He was ex-president of the American Therapeutic Society, ex-president of the New York Pathological Society and ex-president (two terms) of the Medical Society

of Greater New York Dr Satterthwaite was one of the earliest members of the American College of Physicians, and maintained an active interest in the College throughout his life

TRUE EDGECOMB MAKEPEACE

True Edgecomb Makepeace, M D, born in Chesterville, Maine, on April 4, 1891, died while administering to the need of a patient in Farnington, Maine, on November 6, 1934

Dr Makepeace graduated from Bowdoin in 1912 and from the Bowdoin Medical School in 1917, where, after postgraduate work at the Harvard University Medical School, he served as instructor

There followed a year's internship at the Central Maine General Hospital, and he became a member of the staff of the Franklin County Memorial Hospital, serving faithfully and most efficiently up to the time of his death

The doctor was an active member of the Maine Medical Association, a Fellow of the American Medical Association and had been advanced to Fellowship in the American College of Physicians in April 1934

A respected elder colleague of Dr Makepeace has expressed himself as follows "I had known Dr Makepeace since he was a boy and associated with him a good deal It was always a pleasure to work with him He was a scholarly kind of medical man and had quite decided opinions but always gave courteous consideration to the opinions of others I think he was becoming expert in radiography and I had the highest regard for the honesty of his judgment He was square and honorable in his relations with other people and with doctors I feel personally that I have lost a valuable colleague and a good friend"

Dr Makepeace's passing is a distinct loss to the Maine profession Would that there were more men as "square and honorable"!

E W GEHRING, M D, F A C P,

Governor for Maine

PAUL GALPIN SHIPLEY

Paul Galpin Shipley, M D, F A C P, died suddenly on September 12, 1934, from heart disease Dr Shipley was born in New Haven, Connecticut, October 17, 1888 He received his medical degree from Yale Medical School in 1913, after which he spent a year as Assistant in Biology at Yale University He then became a member of the Department of Anatomy at the Johns Hopkins University where he worked under Dr Franklin P Mall His studies on the structure of bone led him to become associated with Dr John Howland, Professor of Pediatrics, and since 1917 he has been a member of the Department of Pediatrics, holding the position of Associate Professor of Pediatrics for the past eight years

Dr Shipley made many valuable contributions to the study of experi-

mental and clinical rickets and other diseases of bone. Much of this work was reported in conjunction with Dr. E. A. Park, Dr. E. V. McCollum and Miss Simmons. He was responsible in part or in whole for 55 contributions to American and foreign medical journals. One of his recent publications was concerned with the description of a method of demonstrating lead in the blood by spectrographic examination. He was a member of the American Pediatric Society, the Society for Clinical Investigation and Fellow of the American Academy of Pediatrics. In March 1931 he became a Fellow of the American College of Physicians.

Although Dr. Shipley was primarily interested in laboratory research he devoted a good deal of time to the wards in the Harriet Lane Home for Invalid Children where his clinical opinion was highly thought of. He was one of the first to recognize and report tick-bite fever in the East. He was actively engaged in teaching members of the third and fourth year classes at the Johns Hopkins Medical School. The medical profession and the American College of Physicians have suffered a real loss by the sudden death of this able investigator and teacher of medicine.

HENRY M. THOMAS, JR., M.D., F.A.C.P.,
Governor for Maryland

HUGH MacKAY

Dr. Hugh MacKay (Fellow) died at his home in Winnipeg, October 12, 1934, in his seventieth year.

Dr. MacKay was born at West Zorra, Oxford County, Ontario, attended the Collegiate Institute at Woodstock and graduated in medicine from the Manitoba Medical College in 1895. For some years, he practiced general medicine and surgery, but in 1914 confined his practice to dermatology. For some years, he practiced at Carberry before removing to Winnipeg. He was one of the first practitioners in that city to employ radium as a therapeutic agent, and his knowledge of skin diseases was responsible for his appointment as professor of dermatology on the Faculty of Medicine of the University of Manitoba. He was a member of the honorary staff of the Winnipeg General Hospital, a member of the Winnipeg Medical Society, Manitoba Medical Association and the Canadian Medical Association. He became a Fellow of the American College of Physicians during 1920.

"Dr. MacKay was a man of much kindness of heart and integrity of life."

MERCHANT W. COLGIN

Merchant W. Colgin, M.D., F.A.C.P., died at his home in Waco, Texas, July 15, 1934, after an illness of almost a year. His initial symptoms, which occurred in the summer of 1933, resulted from malignant hypertension which was rapidly progressive and ended in uremia.

Dr Colgin graduated from the Medical Department of Vanderbilt University in 1905, and after an internship at St Vincent's Hospital in Birmingham, Alabama, he returned to his home in Waco, Texas, where he practised continuously until his death. In addition to his efforts in behalf of organized medicine in general, and internal medicine in particular, he took an active interest in civic affairs. He was a charter member of the Texas Internist's Club, and had been a Fellow of the American College of Physicians since 1923. In association with his brother, Dr I E Colgin, he organized the Colgin Hospital and Clinic in 1921, an institution with which he was connected up to the time of his death. Dr Colgin was first and foremost an internist, but he became interested in the medical aspects of life insurance and had for a number of years served as Medical Director of the Texas Life Insurance Company.

Dr Colgin was an outstanding physician who was held in highest esteem by his many friends and patients, not only on account of his high professional qualifications but also because of his pleasing and amiable personality. In his passing the cause of internal medicine in his native state has sustained a distinct and regrettable loss.

CHARLES T STONE, M D , F A C P ,
Governor for Texas

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HEART BLOCK DUE TO CALCAREOUS LESIONS OF THE BUNDLE OF HIS

REVIEW AND REPORT OF A CASE WITH DETAILED HISTOPATHOLOGIC STUDY*

By WALLACE M. YATER, M.D., F.A.C.P., and VIRGIL H. CORNELL, MAJ
M.C., U.S.A., F.A.C.P., *Washington, D.C.*

CONSIDERING the fact that only 47 cases of established complete heart block reported in the literature have been sufficiently thoroughly studied to be acceptable as conclusive, we believe that further careful studies of this subject are important. These 47 cases have been tabulated by Yater, Cornell and Claytor¹. In nine cases the auriculoventricular dissociation was due to calcareous or fibrocalcareous lesions of the bundle of His. Together with fibrosis of the bundle or bundle and branches, fibrosis of the two bundle branches without lesions of the main bundle, and gummatous invasion of the bundle, this type of lesions constituted one of the most common causes of complete heart block.

In order to determine whether the calcific lesions causing heart block possess common characteristics and perhaps similar etiology and pathogenesis, we have carefully reviewed the reports of the nine cases of established complete heart block alluded to and of one case of Yater and Willis² of intermittent heart block associated with the same type of lesion. A brief résumé of each of these cases is given below.

1 *Bonnunger*,³ and *Monckeberg*⁴ (1908). A man, aged 67 years, had had Adams-Stokes attacks for several years. Toward the end long attacks of asystole occurred, some as long as three minutes, one reported to have lasted eight minutes. The ventricular rate was 30 to 45 per minute. Electrocardiograms (not published) confirmed the complete A-V dissociation. The heart was enlarged. The coronary arteries were not significantly altered. There was severe sclerosis of the aortic and mitral valves, especially the aortic leaflet of the mitral, due to fibrosis and calcification. The latter was most marked in the bottom of the sinuses of Valsalva and at the base of the aortic leaflet of the mitral valve, and extended from both places into the membranous portion of the interventricular septum, which was diffusely thickened. Careful histologic examination showed that the portion of the calcium mass extending from

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From the Georgetown University School of Medicine and the Army Medical Museum

the mitral valve completely interrupted the A-V bundle in its midportion. The terminal portion and origins of the bundle branches were normal. The calcium mass was surrounded by dense fibrous tissue containing lymphocytes. Small masses of calcium were present also in the myocardium of the interventricular septum.

2 *Nagayo*⁵ (1909) A woman, aged 79 years, had Stokes-Adams attacks for two (?) years before death. Sphygmograms (not published) always showed complete heart block (auricular and ventricular rates not stated). There was severe coronary artery sclerosis. A mass of calcium was imbedded in the upper edge of the myocardium of the interventricular septum at the base of the aortic leaflet of the mitral valve, and there were smaller masses in this valve. Careful histologic examination showed that the main calcium mass strongly compressed the A-V bundle as it traversed the membranous portion of the septum, and in one area completely destroyed it. The bifurcation and upper portions of the bundle branches were normal.

3 *Gibson and Ritchie*⁶ (1909) A man, aged 76 years, had Adams-Stokes attacks for three years, during which time the pulse rate was normal except during attacks, when it went as low as 16 per minute. After this, the pulse rate was constantly 28 to 34 per minute, and there were no more attacks in the remaining four years of life. Polygrams (published) showed complete A-V block. The heart was moderately hypertrophied and dilated. The aorta and coronary arteries were dilated. The mitral valve was thickened and calcareous, mainly at the base of the aortic leaflet. The aortic valve was thickened but not deformed. Careful histologic examination showed dense fibrous transformation of the interventricular septum at the juncture of the membranous and muscular portions, with deposits of calcium therein. This fibrocalcareous lesion largely replaced the A-V node and the first portion of the A-V bundle.

4 *Bishop*⁷ (1910), and *Oppenheimer and Oppenheimer*⁸ (1914) The patient a man aged 75 years, died suddenly after severe attacks of vertigo and tinnitus and of syncope, which he had had for over a year. The pulse rate was 20 to 36 per minute. Jugular and radial sphygmograms (published) showed complete heart block. The heart was not enlarged. There was severe coronary artery sclerosis. A large mass of calcium extended from the aortic leaflet of the mitral valve into the membranous portion of the interventricular septum. The aortic valve was thickened but not deformed. Careful histologic study showed that the calcium mass lay directly across the path of the bundle of His at its bifurcation and completely separated it from the origins of the bundle branches. Just before this point the bundle was fibrotic and contained small round cells. All small coronary arteries seen were considerably thickened.

5 *Momad-Kriohn*⁹ (1911) A woman, aged 75 years, had had attacks very suggestive of Adams-Stokes seizures for about a month. Until the last few days of life the pulse rate was usually about 60 per minute, but at times it would drop to 36. For about a week before death it apparently remained at this rate or lower (no tracings published). Death occurred in a convulsive seizure. The heart was somewhat enlarged. The mitral leaflets were infiltrated with calcium, and there were small deposits of calcium in the aortic valves. From the line of attachment of the aortic leaflet of the mitral valve a series of small masses of calcium spread out along the juncture of the membranous and muscular portions of the interventricular septum. Serial sections of this region showed the bundle of His compressed in its middle portion by masses of calcium above and below it. The bundle for some distance was very fibrotic and infiltrated with lymphocytes and plasma cells.

6 *Hoffmann*¹⁰ (1914) and *Monckeberg*¹¹ (1916) A man, who had had Adams-Stokes attacks for five years, died at the age of 56 years. The ventricular rate had been 28 per minute except when he had tonsillitis, when it rose to 48. Polygrams and electrocardiograms (published) showed complete heart block with right bundle-

branch block⁴ The heart was moderately enlarged There was sclerosis of the aorta, coronary arteries, aortic valve, mitral valve and pulmonary artery A mass of calcium extended down from the base of the aortic valve into the membranous septum Careful histologic examination showed the bundle of His completely destroyed by the calcium mass ("calcified thrombus") just before the point of division The upper portions of both bundle branches were very fibrotic

7 *Starling*¹² (1921) and *Lewis*¹³ (1922) A man, aged 51 years, had had "fits" from November 1918 to May 31, 1919, during which time his pulse rate had been 60 to 80 per minute with normal a-c intervals except during the attacks Swallowing sometimes caused the dropping of several ventricular beats but not after atropine was given After May 31, 1919, there were no more "fits," and the pulse varied from 41 to 48 per minute with the auricular rate of 80 to 110 per minute as shown by polygrams (published) One day the patient dropped dead Both ventricles were hypertrophied and dilated The aortic valves were thickened at the edges by fibrous tissue and small masses of calcium The anterior cusps were fused by calcification, and a mass of calcium extended from this point down into the left ventricle The coronary arteries were dilated and atheromatous Careful histologic study showed the A-V node to be normal There was dense connective tissue about the first part of the bundle The second half of the bundle was flattened, a little fibrous and contained small groups of lymphocytes Near the bifurcation the bundle encountered the calcium mass in the septal muscle and was heavily damaged by fibrosis with lymphocytic infiltration The upper part of both bundle branches was fibrous, as was the upper part of the septum

8 *Yater and Willis*² (1929) A man, aged 74 years, had had Adams-Stokes attacks for three months The ventricular rate was 40 per minute Electrocardiograms (published) revealed multiple transitions which ranged from periods of normal sinus rhythm through varying grades of A-V block to remarkably long periods of asystole Severe seizures of convulsive syncope became very frequent shortly before death, one lasting four minutes with complete cardiac standstill The heart weighed 388 grams and showed moderate coronary artery sclerosis There was a bar of calcium in the muscular portion of the interventricular septum below the juncture of the membranous and muscular portions most voluminous at the line of attachment of the aortic leaflet of the mitral valve The bar of calcium lay beneath the bundle of His and greatly compressed the anterior half, which was invaded by fibrous tissue and some lymphocytes and plasma cells The first portions of both bundle branches were fibrous, especially the right

9 *Mahaim*¹⁴ (1931) The patient was a man, aged 63 years, who had had dyspnea and syncopal attacks The pulse rate was 36 per minute Polygrams (published) showed complete heart block with auricular flutter or flutter-fibrillation and transitory bigeminy There was a calcified nodule at the base of the aortic cusp of the mitral valve extending out into the membranous septum Careful histologic examination showed multiple calcium masses in this region The bundle of His was dislocated by the calcium and separated from the A-V node by a superior prolongation of the calcium mass noted grossly The right bundle branch was separated from the main bundle and destroyed lower by fibrosis, while the anterior division of the left branch was destroyed by fibrocalcereous lesions At the origin of these lesions there was stenosis of the right coronary artery Small masses of calcium were disseminated through the upper part of the interventricular myocardium

10 *Don, Grant and Camp*¹⁵ (1932) A man, aged 68 years, had a pulse rate of 30 to 40 per minute, and electrocardiograms (published) showed complete A-V dissociation with great variation in the ventricular complexes from right to left bundle-branch block types, both abrupt and gradual He died suddenly The heart weighed 475 grams Both ventricles were hypertrophied and dilated There was

* The old terminology of bundle-branch block is used in this paper

some coronary artery sclerosis without occlusion. A large nodule of calcium was located at the juncture of the aortic leaflet of the mitral valve with the interventricular septum and embedded in the myocardium of the septum. Careful histologic study showed the bundle of His to be destroyed by the calcium at its bifurcation and separated from the bundle branches.

These cases may now be compared with the one which we are reporting

CASE REPORT *

Clinical Case Record The patient, a retired Army officer, aged 69 years, entered Walter Reed General Hospital, Washington, D. C., on January 15, 1933 and died January 21, 1933. His family history was irrelevant. Since 1914 he had been consistently treated for syphilis which had been acquired in 1902. He was known to have a fusiform aneurysm of the aorta, and his blood Wassermann reaction was always positive. Except for slight dyspnea on exertion, productive cough and occasional precordial discomfort, he felt quite well until December 24, 1932, which was four weeks before he died, when he began to have convulsive seizures, severe dyspnea, more intense precordial pain and swelling of the feet and ankles. His general strength failed rapidly, and he was confined to bed. Urination became burning and difficult, and the amount of urine small. He was emaciated and had a marked uremic odor of the breath. There were bruises over the entire body and bad ecchymoses

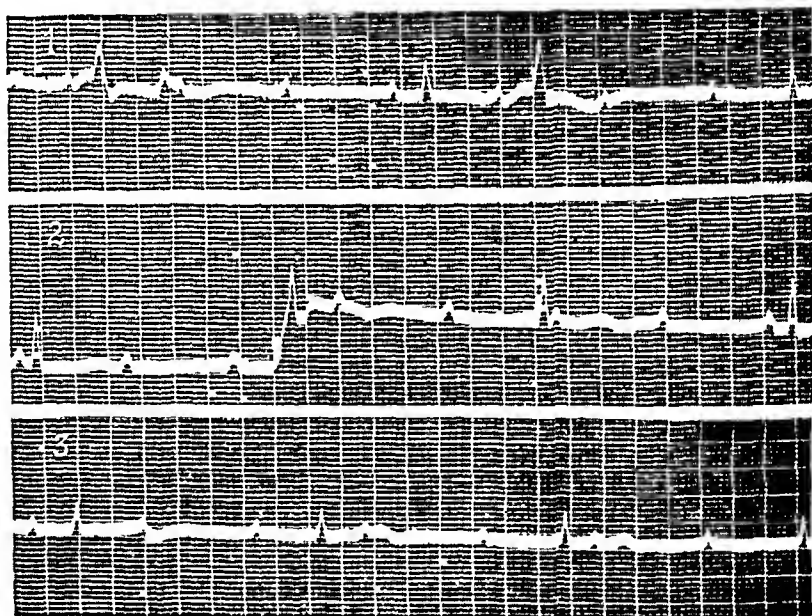


FIG 1 Conventional leads of the electrocardiogram, showing complete auriculoventricular dissociation with premature contractions

about the eyes and face. A bedsore was present at the end of the spine. The peripheral arteries were firm, beaded and tortuous. There was edema of the feet and ankles. The heart was slightly enlarged, and the ventricular rate was 40 to 45 per minute. A systolic and a diastolic murmur were present at the aortic area. There were moist rales at the bases of the lungs posteriorly. The abdomen was normal.

* Army Medical Museum Accession No 40536

The prostate gland was enlarged, "boggy" and tender. The hemoglobin was 80 per cent, the erythrocytes numbered 4,220,000 and the leukocytes 15,000 per cu mm of blood, with 83 per cent polymorphonuclear neutrophils. The urine contained a few casts and a great deal of pus. The urea nitrogen was 40.5 mg per 100 cc of blood. The blood Wassermann reaction was one plus, the Kahn reaction three plus. A roentgenogram of the chest showed a fusiform aneurysm of the arch of the aorta. An electrocardiogram showed the presence of complete heart block with auricular rate of 90 and ventricular rate of 50 per minute (figure 1). There were numerous premature ventricular beats from several foci. The T-wave was diphasic in Lead I and upright in Leads II and III. The congestion became progressively worse. On January 18 a severe convulsive seizure was followed by hemiplegia of the right side. On January 21 severe convulsive seizures occurred with violent movements of the left side of the body, the heart rate became slower and Cheyne-Stokes respiration ensued. Death occurred the same day in a convulsive attack.

*Necropsy** Inasmuch as the main organ of interest to us was the heart, we shall merely note the anatomical diagnoses other than cardiac.

Arteriosclerosis, generalized, severe, with involvement of the cerebral and coronary arteries especially.

Pul edema and congestion.

Multiple areas of anemic softening of the cerebral cortex of the parietal and occipital lobes, left.

Syphilitic mesaortitis and aortic arteriosclerosis, with aneurysmal dilatation of the arch of the aorta, dilatation of the innominate artery and obliteration of the origin of the left carotid artery.

Moderate nephrosclerosis.

Prostatic hypertrophy, interstitial and adenomatous, with some urinary obstruction.

Dilatation, retention, trabeculation and small cellules of the urinary bladder, with chronic suppurative cystitis.

Senility, indicated by atrophy of the skin, etc.

Decubitus ulcer, sacral.

Subcutaneous edema, generalized, and especially of the right arm and leg.

Multiple abrasions of the body.

Pleural effusion, 800 cc left, 900 cc right, with depression of the diaphragm.

Partial atelectasis of the lungs.

Bronchopneumonia, acute, suppurative, terminal, bilateral, moderate.

Pulmonary edema and congestion, moderate.

Chronic passive congestion of the liver and spleen.

Emaciation and muscular atrophy.

Edentulous condition of the mouth.

Lymphadenitis chronic, tuberculous, inactive, of the peritracheal nodes.

Gross Description of the Heart The heart weighed 430 grams, with moderate hypertrophy of the left ventricle. The pericardium and myocardium appeared normal. The endocardium and valves appeared normal except for the aortic and mitral valves. The aortic leaflet of the mitral valve was thickened, mainly by an elongated, calcified plaque, 2.5 cm long, which extended out into the leaflet from its junction with the posterior cusp of the aortic valve. This plaque also extended far forward as an elongated pyramidal verrucous mass of calcium into the interventricular septum between the membranous and muscular portions, but it lay more in the muscular portion (figure 2). The greatest bulk of the mass of calcium was located at the line of attachment of the aortic cusp of the mitral valve, and just anterior to this it made a visible projection of about 0.7 cm into the cavity of the left ventricle. The

* Performed by Major Hugh W. Mahon, M.C., U.S.A.

aortic valve presented calcification along the line of attachment to the aorta, and there was some fusion of the commissure between the anterior cusps and broadening and flattening of the commissure between the right anterior and the posterior cusps. The aortic sinuses were deepened and pouch-like. The orifices of the coronary arteries were surrounded by an atheromatous deposit but were not narrowed. The left coronary artery was thick-walled and tortuous, but its lumen was patent throughout. The right circumflex artery showed extensive atherosclerosis, with reduction of the lumen in its proximal third by about one half and in its middle third almost to obliteration, but beyond this its lumen was not so constricted.



FIG 2 Roentgenogram of the opened heart after necropsy, showing the calcium mass in the interventricular septum

Histopathologic Examination of the Heart Two adjacent, large blocks of tissue were excised from the upper portion of the interventricular septum, which included most of the membranous portion and about the upper one-sixth of the muscular portion. These blocks included most of the calcium mass, the A-V node and bundle and the upper portions of the bundle branches. The blocks were called 1 and

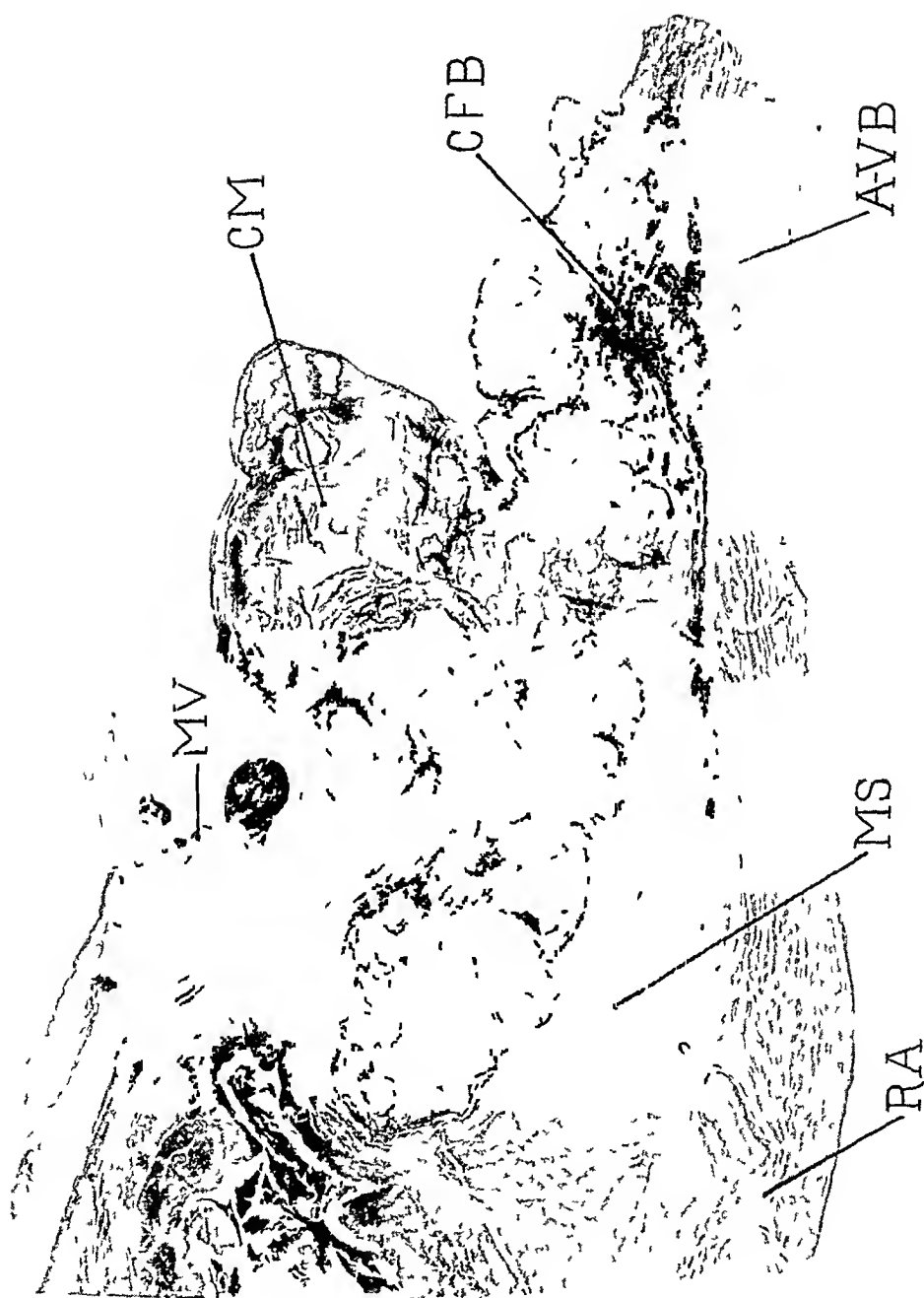


FIG 3 Section 721 of block 1, showing the calcium mass, CM, in the interventricular septum, and the atrioventricular bundle, A-VB, passing through the central fibrous body, CFB MV, mitral valve, MS, muscular portion of the septum, RA, musculature of the right auricle $\times 10$

oughly explained by the study of blocks 1 and 2 the bundle branches were not examined in the remainder of their course. The myocardium appeared to be quite normal, and the only intra-myocardial arteries altered to any extent that were observed were those already mentioned in the vicinity of the mass of calcium.

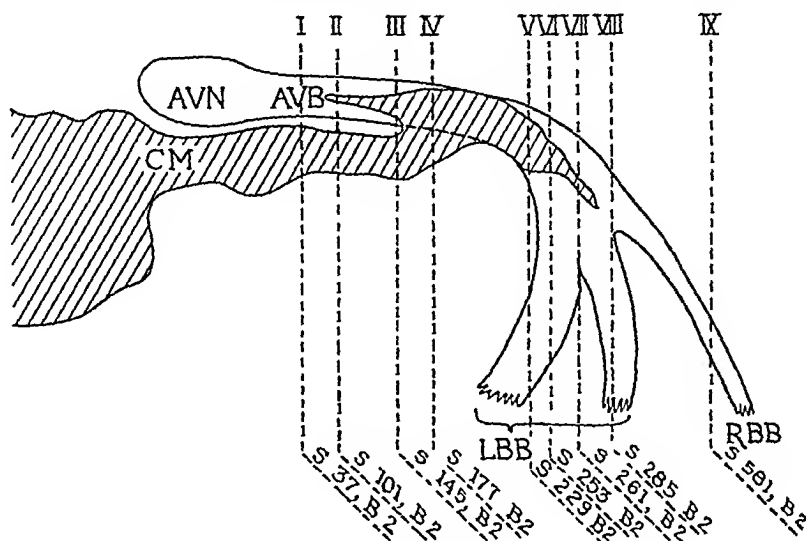


FIG 5 Diagram showing the relationship of the calcium mass, CM, to the auriculo-ventricular node, AVN, the bundle of His, AVB, the left bundle branch, LBB, and the right bundle branch, RBB. The vertical interrupted lines show the planes of the sections reproduced in figure 4, with corresponding Roman numerals above and section and block numbers below.

Summary of Examination of the Heart The heart was moderately enlarged. The pericardium and myocardium grossly were apparently normal. There was moderately severe sclerosis of the left coronary artery and almost complete occlusion by sclerosis of the circumflex branch of the right coronary artery. A large, verrucous mass of calcium was located at the base of the aortic leaflet of the mitral valve which extended out into this leaflet and also forward into the interventricular septum, mainly in the upper edge of the muscular portion. There was also calcification along the line of attachment of the aortic valve, with some fusion of the anterior cusps of this valve. Serial sections through the portion of the interventricular septum containing the main part of the conduction system showed the latter structure to be normal except in the middle third and part of the anterior third of the bundle of His, which was invaded for a distance of 1.8 mm by the calcium mass lying mainly below it. At about the middle of this portion of the bundle the calcium had completely replaced it. The end and bifurcation of the bundle and the upper portions of the bundle branches were apparently normal. There was some fibrosis of the bundle with some lymphocytic infiltration surrounding the calcium mass. Some of the smaller arteries in the region of the calcium mass were very sclerotic and were occluded in places. The myocardium and the other intra-myocardial arteries were essentially normal.

DISCUSSION

The 10 cases of heart block which we have collected and abstracted from the literature and the one we have just reported show striking similarities. All of the patients were more than 50 years of age at the time of death.

Only two were in the sixth decade of life and five were in the eighth decade. Nine of the patients were males. Ten had had Adams-Stokes attacks, and most of them died in an attack. In one case the clinical history was not recorded. The accumulation of calcium in nine cases was present essentially and mainly in the same location, namely, at the base of the aortic leaflet of the mitral valve and extending out into the interventricular septum at the juncture of the membranous and muscular portions. In two cases it extended down into the septum mainly from the aortic valve. Either the auriculoventricular node or bundle was completely destroyed at one point or another by the invasion of calcium (in seven) or mainly by fibrosis due to compression by the calcium (in four).

The presence of coronary artery sclerosis was not so constant as the advanced age of the patients and the location of the calcium mass. It was present in at least seven cases, but it was of severe grade apparently in only three. The myocardium showed significant fibrosis in very few. From these facts it is impossible for us to believe that the calcific lesions were primarily due to vascular disease. It is true that in some cases the smaller coronary arteries in the region of the calcium mass were severely affected by sclerosis, but this could have been just as probably a change secondary to the deposition of calcium as preliminary to and causative of it.

The presence of calcium at the base of the aortic leaflet of the mitral valve is not uncommon in the hearts of older individuals, and extension of this lesion into the interventricular septum may occur without involvement of the conduction system, although the chance for such involvement when the calcareous lesion is extensive is great because of the location of the bundle of His.

It seems probable to us that the deposition of calcium in this region is usually due to stress and strain. The main mass of the heart is really hanging from the membranous portion of the interventricular septum, and the point of junction of this part of the septum with the muscular portion of the septum and the aortic leaflet of the mitral valve is undoubtedly one of great stress and strain, both during systole and diastole. As age advances and the vascularity of the heart is reduced by natural causes calcium becomes deposited at this point. In rare cases, as perhaps in those of Hoffmann and Monckeberg and of Starling and Lewis, calcification of endocarditic thrombi of the aortic valve may be the manner of pathogenesis.

These cases, particularly that of Yater and Willius, indicate that the bundle of His may be seriously damaged and still function normally from time to time. Apparently only a few fibers are necessary for normal functioning. On the other hand, vagal action or toxic substances may so depress a partially damaged bundle as to prevent it from functioning.

It is interesting to note that although the conduction system apparently functions like nervous tissue it is anatomically muscular tissue. The auriculoventricular bundle may be completely destroyed in one portion and yet

be quite normal above and below this point, as is so well demonstrated by the case we have reported

SUMMARY AND CONCLUSIONS

1 The acceptable cases reported in the literature of auriculoventricular heart block due to calcareous or fibrocalcareous lesions of the conduction system have been reviewed, and a new case has been reported

2 The calcium mass in such cases usually extends from the base of the aortic leaflet of the mitral valve into the interventricular septum at the juncture of its membranous and muscular portions and invades the auriculoventricular node or bundle, which lies in this region

3 The subjects of this disease are older individuals who do not necessarily have significant coronary artery sclerosis, and whose hearts usually do not show evidence of endocarditis

4 The pathogenesis in most cases is probably the deposition of calcium at the point of greatest stress and strain in the heart, in other cases it may be due to calcification extending down into the membranous septum from old aortic endocarditis

5 The conduction system above and below the point of destruction is frequently quite normal, thereby demonstrating the non-nervous structure of this system

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QUANTITATIVE STUDIES ON INCREASED POTENCY OF LIVER EXTRACT BY INCUBATION WITH NORMAL HUMAN GASTRIC JUICE

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THE therapeutic effectiveness of liver and fractions of liver in the treatment of pernicious anemia is well established. Minot, Cohn, Murphy, and Lawson¹ demonstrated that although slight reticulocyte responses followed the daily feeding of 60 grams of cooked liver, near-maximal responses did not usually occur unless from 150 to 200 grams of cooked liver were fed. Minot, Murphy, and Stetson² stated that "There is apparently some minimal amount of liver in the vicinity of 60 gm of cooked liver, which is a necessary daily amount to produce a distinct reticulocyte reaction when the red blood cells are about 1 25 million per cu mm." Minot, Cohn, Murphy, and Lawson,¹ and Zervas³ have demonstrated that the amount of Liver Extract No 343 derived from 300 grams of whole liver (from 12 to 14 grams of the dried powder) is about the minimal amount required to produce maximal reticulocyte reactions when fed daily to patients with pernicious anemia in relapse. Castle and his associates⁴ later demonstrated that beef muscle, beef muscle protein, or yeast, after incubation with normal human gastric juice produced reticulocyte reactions when fed to patients having pernicious anemia, although the beef muscle, beef muscle proteins, yeast, and the gastric juice were ineffective when fed alone. Sharp,⁵ Sturgis and Isaacs,⁶ Conner,⁷ Wilkinson,⁸ and others have since shown that preparations of hog gastric tissue are likewise effective when fed daily in amounts equivalent to from 200 to 300 grams of fresh stomach tissue (from 30 to 40 grams of desiccated material). Following these studies Reimann and Fritsch⁹ reported a thirty-fold increase in potency of whole liver by its digestion in normal human gastric juice. They reported that as small amounts as 10 grams of whole liver after incubation for two hours with 10 cc of human gastric juice produced near-maximal reticulocyte responses when fed daily to patients having pernicious anemia. Walden and Clowes¹⁰ obtained an active preparation by the interaction of liver or liver extracts with small amounts of hog gastric tissues. Barnett and Thebaut,¹¹ however, were apparently unable to increase the activity of liver by its digestion with normal human gastric juice.

It is the purpose of this paper to report the results of the daily feeding to patients with pernicious anemia in relapse of varying subminimal amounts of Liver Extract No 343 that had been incubated at 40° C for from two to

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four hours with varying amounts of normal human gastric juice. These studies are part of a series attempting to determine the mechanism of the apparent increase in potency of liver and liver extracts, and to determine the relationship of the intrinsic factor of Castle, the active principle of liver, and extrinsic factors in the liver to this activation. Portions of these data have been presented elsewhere^{12, 13}

METHODS

All of the test materials were administered daily by mouth for 10 days to patients having pernicious anemia in relapse. During the periods of study daily red blood cell counts, hemoglobin (Newcomer) determinations, and reticulocyte counts were made. The patients received meat-free, low vitamin B₁₂ diets during the test periods. The noon meal was given between 11 and 11 30 a m and the patients then received no food until 6 30 p m. The liver extract-gastric juice digests were brought to pH 5.0 by the addition of sodium hydroxide immediately before the administration to the patients at 4 30 p m. The patients having slight or no reticulocyte responses or clinical improvement responded to known potent materials administered by mouth before the experiments were considered negative.

RESULTS

The responses of the red blood cells, hemoglobin, and reticulocytes to the various preparations are recorded in table 1. It can readily be seen that there was no response of the blood to the amount of liver extract derived from 100 grams of whole liver (4.5 grams of powder), to 150 c c of normal human gastric juice, or to 0.5 or 1.0 gram of liver extract which had been incubated with 100 c c of gastric juice. There was a very slight response of the reticulocytes (3.4 per cent at a red blood cell level of 1.37 million) but no clinical response when 2 grams of liver extract after incubation with 100 c c of gastric juice were fed to Case 5. There was a rise in reticulocytes up to 18.8 per cent (at a red blood cell level of 1.60 million) when Case 4 received daily 3 grams of liver extract which had been incubated with 100 c c of gastric juice. However, there was little rise in the red blood cells, and the clinical improvement was not marked. The administration of Extralin was followed by another reticulocyte rise up to 13.0 per cent (at a red blood cell level of 2.63 million) and a very satisfactory clinical improvement. An apparently maximal reticulocytosis (23.4 per cent at a 1.53 million red blood cell level) followed the administration of 4 grams of liver extract which had been incubated with 100 c c of gastric juice. A satisfactory clinical improvement followed this response, although a further rise in reticulocytes up to 6.2 per cent at a 3.14 million red blood cell level followed the subsequent administration of Extralin. There were maximal reticulocyte responses (24.4 and 21.2 per cent at red blood cell counts of 1.67 and 1.69 million, respectively) and satisfactory clinical improvement when 4.5 grams of liver extract (the amount derived from 100

grams of whole liver) were incubated with 100 c c of gastric juice and fed to Cases 1 and 2

Slight but definite reticulocyte responses followed the administration of 4.5 grams of liver extract which had been incubated with 10 and 25 c c of gastric juice, while the response to 4.5 grams of liver extract incubated with 50 c c of gastric juice was very nearly maximal (17.2 per cent with a red blood cell count of 2.00 million)

TABLE I

The Responses of the Red Blood Cells, Hemoglobin (Newcomer), and Reticulocytes of Patients Having Pernicious Anemia to Various Test Materials and to a Known Potent Therapeutic Agent (Extralin)

| Days | Case 1 | | | Case 2 | | | Case 3 | | |
|------|--------------------|----------|----------|--------------------|----------|----------|--------------------------|----------|----------|
| | 4.5 gm L E * | | | 150 c c G J † | | | 0.5 gm L E + 100 c c G J | | |
| | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % |
| 0 | 1,750,000 | 39.5 | 0.3 | 1,440,000 | 33.0 | 0.7 | 2,870,000 | 70.2 | 2.1 |
| 1 | 1,640,000 | 37.3 | 0.4 | — | — | 1.0 | 2,680,000 | 68.8 | 1.2 |
| 2 | 1,310,000 | 34.4 | 0.1 | 1,310,000 | 31.8 | 0.3 | 2,680,000 | 59.8 | 2.2 |
| 3 | 1,300,000 | — | 1.0 | 1,550,000 | 34.4 | 0.4 | — | — | 1.7 |
| 4 | 1,570,000 | 37.0 | 0.1 | 1,300,000 | 43.0 | 0.6 | — | — | 2.1 |
| 5 | 1,310,000 | 33.0 | 0.4 | 1,370,000 | 35.8 | 0.4 | 2,650,000 | 63.7 | 2.4 |
| 6 | 1,220,000 | 30.7 | 0.8 | 1,270,000 | 30.7 | 0.5 | 2,730,000 | 64.0 | 1.7 |
| 7 | 1,480,000 | 31.9 | 0.8 | 1,350,000 | 34.4 | 0.4 | 2,460,000 | 57.0 | 1.4 |
| 8 | 1,360,000 | 31.5 | 0.7 | — | — | 1.1 | 2,380,000 | 56.4 | 1.1 |
| 9 | 1,210,000 | 30.3 | 0.9 | 1,390,000 | 32.7 | 1.1 | — | 56.4 | 1.2 |
| 10 | — | — | 0.9 | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| 13 | | | | | | | | | |
| 14 | | | | | | | | | |
| 15 | | | | | | | | | |
| 16 | | | | | | | | | |
| 17 | | | | | | | | | |
| 18 | | | | | | | | | |
| | | | | | | | Extralin, caps 4 t i d | | |
| 0 | | | | | | | 2,380,000 | 56.4 | 1.1 |
| 1 | | | | | | | — | 56.4 | 1.2 |
| 2 | | | | | | | — | — | 1.6 |
| 3 | | | | | | | 2,800,000 | 59.3 | 1.1 |
| 4 | | | | | | | 2,390,000 | 61.4 | 1.6 |
| 5 | | | | | | | 2,750,000 | 68.8 | 3.0 |
| 6 | | | | | | | 2,550,000 | 65.5 | 3.6 |
| 7 | | | | | | | 2,230,000 | 58.0 | 3.8 |
| 8 | | | | | | | 2,140,000 | 54.2 | 5.6 |
| 9 | | | | | | | — | — | 4.2 |
| 10 | | | | | | | 2,150,000 | 55.5 | 4.6 |

* Liver Extract No 343

† Gastric Juice

Table 1 continued on next page

TABLE I—*Continued*

| Days | Case 4 1 gm L E + 100 cc G J | | | Case 5 2 gm L E + 100 cc G J | | | Case 4 3 gm L E + 100 cc G J | | |
|------------------------|---------------------------------|----------|----------|---------------------------------|----------|----------|---------------------------------|----------|----------|
| | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % |
| 0 | 1,440,000 | 37.8 | 0.2 | 1,340,000 | 34.7 | 1.2 | 1,360,000 | 33.4 | 0.2 |
| 1 | 1,390,000 | 35.1 | 0.6 | — | — | 1.6 | 1,200,000 | 37.1 | 0.4 |
| 2 | — | — | 0.9 | 1,230,000 | 35.1 | 1.9 | 1,320,000 | 34.4 | 0.2 |
| 3 | 1,370,000 | 31.8 | — | 1,420,000 | 41.5 | 1.7 | 1,160,000 | — | 0.2 |
| 4 | 1,270,000 | 31.8 | 0.4 | 1,600,000 | 38.2 | 1.1 | 1,130,000 | 27.0 | 0.5 |
| 5 | 1,410,000 | 31.2 | 0.9 | 1,510,000 | — | 2.0 | 1,070,000 | 22.9 | 0.9 |
| 6 | 1,120,000 | 38.2 | 1.8 | 2,080,000 | 35.1 | 2.1 | — | — | 5.2 |
| 7 | 1,270,000 | 31.8 | 1.5 | 1,450,000 | 40.0 | 2.8 | 1,430,000 | 26.6 | 12.2 |
| 8 | 1,390,000 | 33.0 | 0.9 | — | — | 2.6 | 980,000 | 29.0 | 16.5 |
| 9 | — | — | 0.6 | 1,370,000 | 37.0 | 3.4 | 1,600,000 | 30.2 | 18.8 |
| 10 | — | — | — | 1,460,000 | 34.7 | 2.1 | 1,400,000 | 30.7 | 16.5 |
| 11 | — | — | — | — | — | — | 1,360,000 | 34.4 | 10.2 |
| 12 | — | — | — | — | — | — | 1,660,000 | 37.3 | 8.0 |
| 13 | — | — | — | — | — | — | — | — | 7.2 |
| 14 | — | — | — | — | — | — | 1,780,000 | 47.8 | 6.7 |
| 15 | — | — | — | — | — | — | — | — | — |
| 16 | — | — | — | — | — | — | — | — | — |
| 17 | — | — | — | — | — | — | — | — | — |
| 18 | — | — | — | — | — | — | — | — | — |
| Extralim, caps 4 t i d | | | | | | | | | |
| 0 | — | — | — | — | — | — | 1,780,000 | 47.8 | 6.7 |
| 1 | — | — | — | — | — | — | 2,050,000 | 49.1 | 6.0 |
| 2 | — | — | — | — | — | — | 1,670,000 | 47.1 | 2.5 |
| 3 | — | — | — | — | — | — | 1,860,000 | 50.8 | 3.0 |
| 4 | — | — | — | — | — | — | 1,790,000 | 54.5 | 3.2 |
| 5 | — | — | — | — | — | — | 1,740,000 | 55.6 | 5.1 |
| 6 | — | — | — | — | — | — | — | — | 10.4 |
| 7 | — | — | — | — | — | — | 2,240,000 | 65.0 | 13.8 |
| 8 | — | — | — | — | — | — | 2,630,000 | 55.0 | 13.0 |
| 9 | — | — | — | — | — | — | 3,000,000 | 64.3 | 6.0 |
| 10 | — | — | — | — | — | — | 2,660,000 | 69.5 | 6.0 |

Table 1 continued on next page

SUMMARY AND CONCLUSIONS

The incubation of Liver Extract No 343 with normal human gastric juice markedly increases the potency of the liver extract. There is, however, a definite relationship between the amounts of liver extract and gastric juice necessary to produce maximal reticulocyte responses when the combination is fed daily by mouth to patients having pernicious anemia. It was found that near-maximal responses did not follow the administration of smaller amounts than 4 grams of liver extract (that derived from approximately 90 grams of whole liver) even after it had been incubated with 100 cc of gastric juice. The responses that occurred after the administration of smaller amounts were distinctly submaximal. To increase the potency

of 4.5 grams of liver extract satisfactorily 50 cc or more of gastric juice were required

This increase in potency of liver extract is not nearly as great as that increase in potency of whole liver reported by Reimann and Fritsch when they incubated whole liver with human gastric juice. They were able to induce nearly maximal responses when they fed daily as little as 10 grams of whole liver which had been incubated with only 10 cc of gastric juice. Minot, Cohn, Murphy, and Lawson were unable to produce near-maximal reticulocyte responses unless the amount of cooked liver derived from approximately 200 to 250 grams of whole liver was fed daily to the patients, yet they stated that "The administration daily of the amount of active principle extracted from 300 grams of liver is sufficient to produce a very

TABLE I—Continued

| Days | Case 5 4 gm L E + 100 cc G J | | | Case 1 4.5 gm L E + 100 cc G J | | | Case 2 4.5 gm L E + 100 cc G J | | |
|------|---------------------------------|----------|----------|-----------------------------------|----------|----------|-----------------------------------|----------|----------|
| | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % |
| 0 | 1,460,000 | 34.7 | 2.1 | — | — | 0.9 | 1,240,000 | 36.2 | 1.0 |
| 1 | 1,460,000 | 43.0 | 2.6 | — | — | 1.2 | 1,160,000 | 35.4 | 1.1 |
| 2 | 1,390,000 | 42.5 | 1.6 | 1,250,000 | 28.5 | 1.7 | 1,250,000 | 36.2 | 0.6 |
| 3 | 1,270,000 | 35.1 | 2.2 | 1,230,000 | — | 2.2 | 1,450,000 | 27.2 | 1.0 |
| 4 | 1,270,000 | 36.6 | 3.0 | 1,350,000 | 33.4 | 2.2 | 1,330,000 | 32.7 | 0.9 |
| 5 | — | — | 14.3 | 1,240,000 | 29.1 | 3.2 | — | — | 4.9 |
| 6 | 1,150,000 | 39.1 | 20.3 | 1,440,000 | 30.5 | 11.2 | 1,760,000 | 36.2 | 14.3 |
| 7 | 1,540,000 | 41.5 | 23.0 | — | — | 20.5 | 1,690,000 | 39.1 | 21.2 |
| 8 | 1,530,000 | 50.6 | 23.4 | 1,670,000 | — | 24.4 | 1,800,000 | 41.0 | 12.8 |
| 9 | 1,840,000 | 41.5 | 17.0 | 1,650,000 | 41.0 | 17.5 | 2,240,000 | 39.1 | 9.2 |
| 10 | 2,090,000 | 50.0 | 8.2 | 1,670,000 | 35.1 | 11.7 | 2,000,000 | 41.9 | 6.8 |
| 11 | 2,550,000 | 54.5 | — | 1,800,000 | 36.7 | 9.8 | 2,150,000 | — | 4.3 |
| 12 | — | — | — | 2,190,000 | 36.1 | 5.9 | — | — | 5.7 |
| 13 | 2,060,000 | 50.6 | 10.0 | 2,170,000 | 43.0 | 9.2 | 2,710,000 | 42.0 | 7.5 |
| 14 | 2,450,000 | 48.4 | 7.0 | 2,390,000 | 44.6 | 5.6 | 2,600,000 | 53.5 | 4.9 |
| 15 | — | — | — | 2,730,000 | 50.0 | 4.4 | 2,520,000 | 52.1 | 2.7 |
| 16 | 2,190,000 | 55.5 | 3.5 | | | | | | |
| 17 | | | | | | | | | |
| 18 | | | | | | | | | |
| | Extralin, caps 4 t i d | | | Extralin, caps 4 t i d | | | Extralin, caps 4 t i d | | |
| 0 | 2,190,000 | 55.5 | 3.5 | 2,490,000 | 52.1 | 2.5 | 2,950,000 | 66.1 | 0.8 |
| 1 | 2,200,000 | 57.3 | 1.9 | 2,800,000 | 47.8 | — | 2,790,000 | 55.5 | 0.3 |
| 2 | 2,120,000 | 53.0 | 1.4 | 3,020,000 | 47.8 | 0.2 | 3,270,000 | 55.5 | 0.9 |
| 3 | — | — | 2.0 | — | 47.6 | — | 3,320,000 | 63.7 | 0.8 |
| 4 | 2,300,000 | 55.5 | 0.4 | 2,430,000 | 44.1 | 1.1 | 3,150,000 | 58.3 | — |
| 5 | 2,370,000 | 56.4 | 1.2 | 2,730,000 | 50.6 | — | 3,110,000 | 56.4 | 1.3 |
| 6 | 2,440,000 | 59.3 | 4.2 | 2,980,000 | 52.9 | 2.1 | 3,450,000 | 65.5 | 0.9 |
| 7 | 2,260,000 | 54.5 | 3.8 | | | | 3,060,000 | 65.5 | 0.2 |
| 8 | 2,600,000 | 60.2 | 6.0 | | | | 3,630,000 | 67.5 | 0.4 |
| 9 | 3,140,000 | 67.4 | 6.2 | | | | 3,520,000 | 66.1 | 0.1 |
| 10 | — | — | 5.1 | | | | 3,960,000 | 84.0 | — |

Table 1 continued on next page

TABLE I—Continued

| Days | Case 6 4.5 gm L E + 10 cc G J | | | Case 6 4.5 gm L E + 25 cc G J | | | Case 7 4.5 gm L E + 50 cc G J | | |
|------|----------------------------------|----------|----------|----------------------------------|----------|----------|----------------------------------|----------|----------|
| | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % | R B C per cu mm | Hgb % | Ret % |
| 0 | 1,670,000 | 31.3 | 0.1 | 1,460,000 | 30.5 | 5.2 | 1,440,000 | 34.7 | 1.0 |
| 1 | 1,730,000 | 31.0 | 0.6 | 1,550,000 | 35.2 | 4.5 | — | — | 0.8 |
| 2 | 1,430,000 | 35.2 | 0.6 | — | — | 6.1 | 1,720,000 | 32.7 | 0.6 |
| 3 | 1,580,000 | 31.4 | 0.6 | 2,020,000 | 34.7 | 8.1 | 1,670,000 | 32.7 | 0.4 |
| 4 | 1,340,000 | 26.0 | 1.0 | 1,610,000 | 39.5 | 3.5 | 1,530,000 | 32.3 | 0.8 |
| 5 | — | — | — | 1,530,000 | 39.5 | 2.3 | 1,790,000 | 37.3 | 2.8 |
| 6 | 1,250,000 | 27.0 | 2.6 | 1,460,000 | 40.4 | 4.4 | — | — | 6.9 |
| 7 | 1,440,000 | 30.8 | 4.8 | 1,520,000 | 42.0 | 5.1 | 1,500,000 | 30.8 | 14.6 |
| 8 | 1,550,000 | 31.4 | 9.6 | 1,560,000 | 42.0 | 2.6 | 1,940,000 | 33.2 | 17.4 |
| 9 | 1,480,000 | 31.8 | 5.3 | — | — | 5.7 | 2,000,000 | 32.7 | 17.2 |
| 10 | 1,460,000 | 30.5 | 5.2 | 1,700,000 | 42.0 | 8.4 | 1,930,000 | 38.6 | 15.6 |
| 11 | | | | | | | 2,150,000 | 41.6 | 14.1 |
| 12 | | | | | | | 2,310,000 | 38.2 | 10.1 |
| 13 | | | | | | | — | — | 13.8 |
| 14 | | | | | | | 2,510,000 | 42.0 | 12.8 |
| 15 | | | | | | | 2,400,000 | 44.6 | 11.6 |
| 16 | | | | | | | 2,370,000 | 47.8 | 7.7 |
| 17 | | | | | | | 2,380,000 | 47.8 | 5.0 |
| 18 | | | | | | | 2,840,000 | 50.6 | 4.3 |
| | | | | Extralin, caps 4 t i d | | | Extralin, caps 4 t i d | | |
| 0 | | | | 1,700,000 | 42.0 | 8.4 | 2,840,000 | 50.6 | 4.3 |
| 1 | | | | 1,810,000 | 42.5 | 8.0 | 2,540,000 | 44.1 | 2.5 |
| 2 | | | | 2,020,000 | 44.1 | 6.3 | — | — | 3.7 |
| 3 | | | | 1,940,000 | 47.8 | 6.9 | 2,630,000 | 47.1 | 1.8 |
| 4 | | | | 2,180,000 | 50.6 | 12.7 | 2,440,000 | 50.6 | 1.5 |
| 5 | | | | 2,170,000 | 49.0 | 11.9 | 2,480,000 | 55.5 | 1.8 |
| 6 | | | | — | — | 13.7 | 2,910,000 | 55.5 | 3.0 |
| 7 | | | | 1,830,000 | 53.0 | 7.7 | 2,980,000 | 50.0 | 3.4 |
| 8 | | | | 1,980,000 | 52.9 | 5.5 | | | |
| 9 | | | | 2,250,000 | 58.3 | 7.6 | | | |
| 10 | | | | | | | | | |

satisfactory response." These facts and subsequent extensive clinical experience with liver extract demonstrate that a goodly portion of the active principle of the liver is contained in the liver extract. It can therefore be assumed that the great difference in the increase in potency of whole liver and liver extract is due to a loss of "an extrinsic factor" in the liver during the process of extraction rather than to a loss of the "active principle" of the liver. In addition it can be assumed that the increase in potency of liver or liver extract is the result of an effect of the type described by Castle and his associates when human gastric juice is allowed to act on beef muscle, beef muscle extracts, and yeast, rather than an actual increase in the active principle originally present in the liver.

The fact that as small an amount as 10 cc of normal human gastric juice will increase the potency of 4.5 grams of liver extract so that slight

reticulocyte responses result when the digest is fed daily to patients having pernicious anemia, must be considered when a quantitative estimation of the amount of intrinsic factor in an abnormal gastric juice is attempted, as by Hartfall and Witts,¹⁴ Spies and Payne,¹⁵ and Beebe and Wintrobe.¹⁶ The use of liver extract (approximately 4.5 grams) would seem to be a better source of the extrinsic factor in such tests, as maximal responses can be expected when sufficient intrinsic factor is present in the gastric juice when liver extract is employed as the extrinsic factor, and this is not always the case when beef muscle or yeast is used.

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THE CORRELATION OF MINERAL METABOLISM AND THE VEGETATIVE NERVOUS SYSTEM IN THYROID DISEASE¹

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FOR the past 50 years medicine has been so dominated by bacteriologic concepts of etiology, that we have become accustomed to look for *the* cause of a given disorder. However, in modern biochemical studies of metabolic diseases we have learned that there is frequently a correlation of various factors in a state of equilibrium. For some time iodine deficiency was stressed as a cause of goiter. During the past century there have been occasional references to the importance of calcium in the water supply as a cause of thyroid disease. Again other investigators have ascribed an important rôle to bacterial contamination of the water supply. However, thyroid disease may be considered the end result of a complex biologic equation which may include one or more factors such as diet, climate, geographic and geologic location, infection, hygienic conditions, emotion, temperature, sex and heredity. In any of these predisposing factors calcium and iodine exert an important influence. In fact, it is now believed that there is normally a state of equilibrium between calcium and iodine which regulates thyroid function (Thompson¹). In the presence of dietary excess in calcium and deficiency in iodine the thyroid gland develops hyperplasia.² With a dietary excess in iodine, the administration of calcium promotes the storage of colloid in the thyroid gland, as I have demonstrated in a previous report.³ This tends to explain the therapeutic properties of calcium in clinical hyperthyroidism.⁴ There is a negative calcium balance in thyrotoxic conditions, as is shown by the increased excretion of calcium in the stool and urine, though the blood calcium is usually normal (Aub⁵). As concerns iodine there is usually a normal blood level of 0.008 to 0.018 mg per cent.⁶ In thyrotoxic conditions the gland becomes depleted of iodine and colloid, while the blood iodine is elevated.

The vegetative nervous system is intimately involved in any consideration of thyroid function. The gland is supplied by fibers from the sympathetic and vagus nerves which terminate in the capillaries and glandular epithelium. Pathologic changes such as shrinkage, vacuole formation, and thickening of the neurofibrillae have been recorded in the superior cervical and celiac ganglia in Basedow's disease (Muller⁷). Friedgood⁸ has discussed the role of the sympathetic nervous system in the pathogenesis of exophthalmic goiter. He reports the finding of inflammation, infiltration, degeneration and fibrosis in the cervical sympathetic ganglia of patients suffering from exophthalmic goiter. Most of the clinical symptoms of thyro-

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From the John McCormick Institute for Infectious Diseases.

toxic conditions may be explained by the alterations in tone of the vegetative nervous system, particularly excessive function of the excitor elements and diminished function of inhibitory elements

For the experimental study of thyroid function we may use histologic methods, which are practical because the specific secretion of the gland, thyroglobulin, is contained in the colloid which accumulates within the acini, and which is readily demonstrated by the usual staining methods. Concerning the microscopic appearance, A. Kocher⁹ notes that goiter with much eosinophilic colloid contains much iodine. The most striking histologic difference between goiters containing much and those containing little iodine is the size of the gland follicles. In a thyroid gland containing a large amount of iodine we find large follicles in great quantity and only a few groups of small follicles, while in a goiter containing little iodine nearly all follicles are small. Such observations, as well as the condition of the follicular epithelium, blood vessels and stroma, aid in the interpretation of morphologic changes in the thyroid gland in terms of its functional activity, especially when the conditions are controlled experimentally. The present study is an attempt to correlate the dietary factors, calcium and iodine with hyperfunction of the vegetative nervous system in their effects on the thyroid gland.

EXPERIMENTS

A series of 50 white rats (150–200 grams in weight) were studied under varying conditions of iodine and calcium intake as well as adrenalin stimulation. Of these, six died early in the course of the experiments, leaving 44 animals for final study. The rats were observed in four groups as follows. Group I, a series of seven normal rats kept for two months on an average laboratory diet (bread, green vegetables) and in one instance on an ideal diet of powdered milk, green vegetables and cod liver oil. This should give a reasonable control group of normal thyroids on average and optimum diet. Group II, a series of 14 rats on a diet of pearl barley and distilled water for a period of two months. This diet is practically iodine free. Studies carried out by Forbes and Beegle¹¹ have demonstrated that there is no iodine present in pearl barley. Group III, a series of 13 rats fed on the iodine deficient barley diet and also stimulated daily by subcutaneous injections of 2 minims of adrenalin (1–1000). Group IV, a series of 10 rats received the barley diet, 3 per cent calcium lactate in the drinking water, and daily injections of adrenalin. At the end of the period of experiment (two months) the rats were chloroformed, the thyroids and trachea immediately dissected out, and fixed in 10 per cent formalin. The tissues were embedded in celloidin, thick sections (10–15 microns) were cut, and stained with hematoxylin and eosin. Thick sections were purposely taken to get an accurate concept of the shape and size of the thyroid follicles. In order to render the results as objective as possible the diameters of the thyroid follicles were measured with an ocular micrometer. By this means 100 follicles

TABLE I

| | Rat 1 | Rat 2 | Rat 3 | Rat 4 | Rat 5 | Rat 6 | Rat 7 | Rat 8 | Rat 9 | Rat 10 | Rat 11 | Rat 12 | Rat 13 | Rat 14 | Average |
|---|---------|---------|---------|-------|---------|---------|---------|--------------------|-------|--------------------|---------|--------|--------------------|--------|----------------|
| Group I Normal controls Average diameter 100 follicles in microns | 174 | 242 | 244 | 224 | 213 | 201 | 239 | | | | | | | | 251 microns |
| Thyroid measurements (each lobe) | 6x3x1 | 6x3x1 | 5x2.5x1 | 6x3x1 | 6x3x1 | 6x3x0.5 | 6x3x2 | | | | | | | | |
| Group II Barley and distilled H ₂ O diet Average diameter 100 follicles in microns | 154 | 59 | 34 | 59 | 41 | 33 | 14 | 24 | 29 | 39 | 29 | 66 | 60 | 42 | 48 microns |
| Thyroid measurements (each lobe) | 7x2x2 | 6x3x2 | 6x2x1 | 5x2x1 | 6x3x1 | 5x2x1 | 6x3x2 | 5x3x2 | 5x3x2 | 5x3x2 | 6x3x2 | 6x2x1 | 6x3x1 | 5x3x1 | |
| Group III Same diet plus adrenalin stimu- lation average diameter 100 follicles in microns | 339 | 395 | 102 | 148 | 390 | 371 | 108 | 97* | 136 | 94* | 128 | 106 | 79* | | 187 microns |
| Thyroid measurements | 5x2x0.5 | 5x2x0.5 | 5x4x1 | 6x3x1 | 6x3x0.5 | 5x2x0.5 | 5x2x0.5 | R 8x5x3 L 8x4x2 | 6x3x1 | R 8x3x2 L 7x3x7 | 6x3x0.5 | 5x4x1 | R 7x3x1 L 7x3x1 | | |
| Group IV Barley plus 3% calcium lactate drinking water plus adrenalin stimulation Average diam- eter 100 follicles in microns | 233 | 238 | 225 | 234 | 212 | 195 | 203 | 207 | 219 | 212 | | | | | 221 microns |
| Thyroid measurements | 6x3x3 | 6x4x2 | 6x2x1 | 7x3x2 | 6x2x2 | 6x2x2 | 6x3x2 | 6x3x2 | 7x3x2 | 7x3x2 | | | | | |

Hyperplastic goiter

were counted in each rat thyroid and the average measurement recorded for each (See table 1) This figure, which I call the follicular index, is an indication of the amount of colloid, and offers a simple method of estimating and comparing colloid content It is particularly valuable in studying the thyroid gland of small animals such as rats and mice, where it is rather awkward to dissect out and weigh the entire gland The gross measurements (length by width by thickness) were also recorded with each rat Most of the lobes measured were symmetrical and one measurement is recorded in the table Where there was a difference the measurements are given for both lobes

DISCUSSION OF RESULTS

As recorded in the table, the normal control rats in Group I had an average follicular diameter of 251 microns Group II on iodine deficient diet showed a follicular diameter of 48 microns (See figures 1 and 2)



FIG 1 Normal rat thyroid, optimum diet High power

This represents a loss of colloid down to 19 per cent of the normal amount Microscopically the sections presented the solid appearance of a non-functioning fetal thyroid gland The epithelium was cuboidal in character There was also a definite capillary hyperemia Group III, which had received an iodine deficient diet and daily stimulation with adrenalin showed an average follicular diameter of 187 microns This indicates that adrenalin, even in the presence of iodine deficiency, stimulated secretion of colloid to such an extent that these glands retained 74 per cent of the normal amount of colloid On gross examination this group showed three hyper-

plastic goiters with average lobe measurements of 8 by 5 by 3 as compared to the normal 6 by 2 by 1. Microscopically these sections were characterized by irregular contour of the follicles with a tendency to infolding of the epithelium, hyperplasia of the follicular epithelium, pycnosis and marked hyperemia. (See figure 3) The areas of hyperplasia were suggestive of



FIG 2 Atrophic thyroid, iodine deficient diet High power

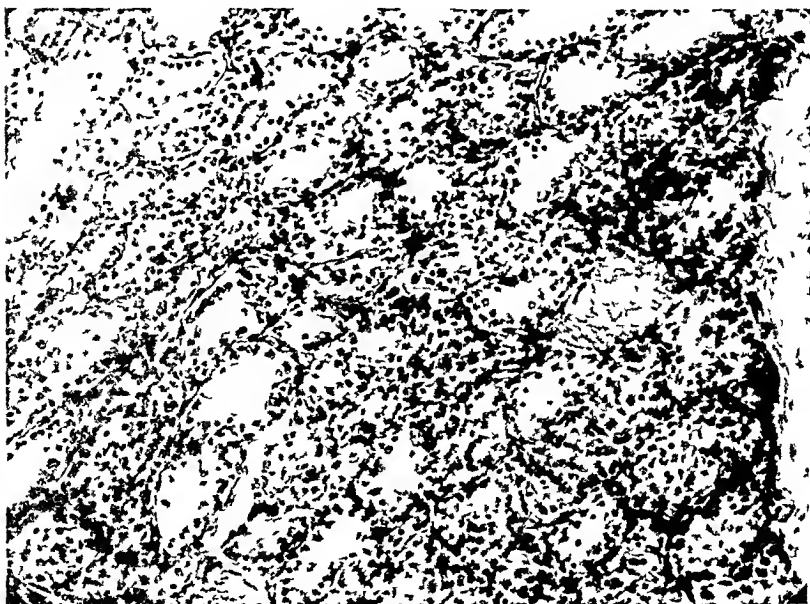


FIG 3 Hyperplastic goiter adrenalin stimulation iodine deficiency

the type seen in exophthalmic goiter. These rats also had varying degrees of exophthalmos as the result of sympathetic stimulation with adrenalin. Group IV, which received iodine deficient diet, adrenalin stimulation, and 3 per cent calcium lactate in the drinking water, showed the greatest amount of colloid storage with an average follicular diameter of 221 microns. This was 87 per cent of the normal value and demonstrated that in the presence of iodine deficiency and overstimulation of the sympathetic nervous system, calcium promotes the storage of colloid in the thyroid gland. Recent studies (Wahlberg¹⁰) indicate that the thyroid cell may secrete its colloid from either pole. Ordinarily the apical portion of the cell secretes the colloid vacuoles which are stored in the follicles. A small amount is secreted by the basal part of the thyroid cell directly into the blood capillaries. In colloid goiter the apical direction of secretion is pathologically increased, but qualitatively similar to the process in normal glands. In thyrotoxicosis the basal secretion mechanism predominates. The clinical improvement after preoperative iodine therapy in thyrotoxicosis corresponds to the reversal of polarity in secretion from basal to apical type with resultant storage of colloid in the follicles. In terms of these recent concepts it seems that in Group IV, calcium administration favored apical secretion in the thyroid epithelium and follicular storage of colloid. Microscopically these sections

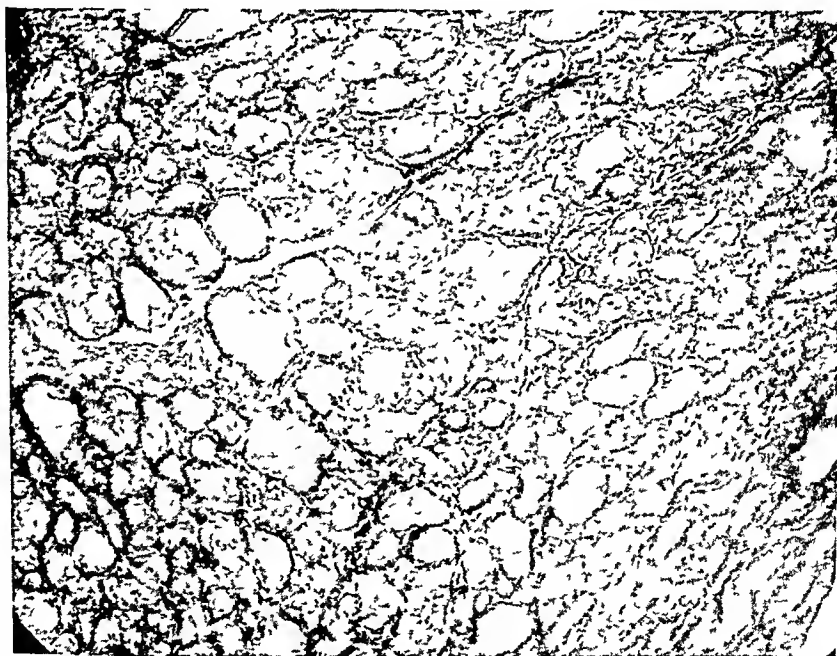


FIG 4 Almost normal storage of colloid. Iodine deficient diet plus 3 per cent calcium lactate plus adrenalin stimulation

looked normal (see figure 4). There was no hyperplasia and no hyperemia. The follicles were distended and the epithelium flattened by the stored eosinophilic colloid. There was a normal stroma. Ordinarily, excessive calcium ingestion associated with an iodine deficient diet causes hyperplastic changes

However, in the presence of adrenalin stimulation there is a storage of colloid approximating normal conditions. This is further proof of the logical indication for calcium in the treatment of clinical hyperthyroidism⁴.

In summarizing the results it may be emphasized that iodine deficient diet caused atrophy of the thyroid gland. This finding confirms the work of Hellwig who concluded that dietary deficiency in iodine is not the essential cause of goiter. Furthermore, it was found that stimulation of the sympathetic nervous system in association with dietary deficiency in iodine induced marked hyperplasia, and in three out of a series of 13 rats, a definite hyperplastic goiter. Finally it was definitely demonstrated that calcium administration promotes the storage of colloid even under such unfavorable conditions as iodine deficiency and overactivity of the sympathetic nervous system induced by adrenalin stimulation.

CONCLUSIONS

1. A new method for estimating and comparing storage of thyroid colloid is described. The follicular diameter is measured by means of an ocular micrometer and the average taken of a large number of measurements.

2. Dietary deficiency in iodine causes atrophy of the thyroid follicles and loss of colloid.

3. Sympathetic stimulation with adrenalin in the presence of iodine deficiency causes hyperactivity of the thyroid epithelium with increased secretion of colloid, hyperplasia, hyperemia, and hyperplastic changes.

4. Calcium administration promotes colloid storage and neutralizes the harmful effects of sympathetic stimulation.

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DISEASES OF THE NERVOUS SYSTEM PRODUCING DYSFUNCTION OF OTHER ORGANS AND DYS- FUNCTION OF OTHER ORGANS PRODUCING OR SIMULATING DISEASES OF THE NERVOUS SYSTEM *

By LEWIS J POLLOCK, M D , *Chicago, Illinois*

DYSFUNCTION of respiration, circulation, secretion, excretion, digestion, growth, metabolism and reproduction occurs alike in diseases of the nervous system and of other organs. The signs and symptoms of such dysfunction necessitate the differentiation of such diseases.

The disturbances of function following encephalitis lethargica illustrate how diversified the dysfunction of the body may become as the result of a disease of the nervous system. To note a few of these disturbances, mention may be made of the disorders of sleep, of somnolence, insomnia and reversal of time of sleeping, of the disturbance in temperature regulation, of hypothermia, associated with general lowering of metabolism, slow pulse and respiration and low blood pressure, of respiratory dysfunction, yawning, inspiratory and expiratory spasm, marked hyperpnea so severe as to produce tetany, of changes in sweating, hyperhidrosis, seborrhea, of secretory disturbances, sialorrhea and lachrymation, polydipsia, polyuria, at times changes in sugar and fat metabolism, glycosuria and adiposity, of menstrual disturbances, amenorrhea, and myasthenia which may be indistinguishable from that of myasthenia gravis.

Functional nervous disease as is found in the neuroses may produce dysfunction of all of the organic functions. Some may be enumerated, although they need not be discussed at this time. The functional manifestations of the digestive system include anorexia, excessive and perverted appetite, dyspepsia, vomiting, dilatation of the stomach, diarrhea, constipation, spasm of the intestines and mucous colitis. Dysfunction of the urinary organs may appear as frequency of micturition, interrupted micturition, painful micturition, polyuria, ischuria and relative anuria, incontinence and rarely retention of urine. The genital troubles of man include spermatorrhea, impotence, absence of ejaculation, premature ejaculation, painful ejaculation and loss of sensations. In women, frigidity, spasms, contractions, pains and amenorrhea. Nasal and laryngeal troubles, spasm of the vocal cords, aphonia, respiratory difficulty, air hunger, and pseudo-asthma occur. Symptoms related to the cardiovascular system are very common such as palpitation, pains, feelings of oppression and the numerous phobias attached to these. Pallor, vasodilatation, disturbances of sweating, cutaneous disturbances, all may be mentioned. In the neuromuscular apparatus, fatigue, weakness, disturbance of equilibrium, tremors and other hyper-

* Read at the Chicago meeting of the American College of Physicians, April 20, 1934

kinesias occur, as well as contractures and "paralysis" Hyperesthesias paresthesias and anesthetics occur, and manifold manifestations of the sense organs may be found Disturbances of sleep are common, as are headache, speech disturbance and psychic change

Organic disease of the nervous system likewise produces change in function of many organs Disorders of the special senses may occur alike in disease of the nervous system and local disease

When loss of smell occurs thought should be given to the possibility of lesions in the anterior cerebral fossa, as olfactory groove meningioma or tumor about the sella Such olfactory disturbances are also often observed following basilar skull fracture Sensations of unpleasant odors and other olfactory or gustatory hallucinations may be the result of lesions in the temporal lobe and occasionally may be misinterpreted as being the result of hysteria or another neurosis or psychosis Defects in vision are of greatest importance in indicating disease of the nervous system and everyone should be familiar with the use of the ophthalmoscope and be able to determine for himself the presence of optic neuritis, optic atrophy and choked disc Very frequently when vision is becoming defective, early recognition of a visual field defect may lead to an early diagnosis of a pituitary adenoma or a brain tumor Sudden blindness, at times in one eye, without evidence of disease in the media or retina, may be the result of a retrobulbar neuritis in multiple sclerosis Scintillating scotomata are the usual precursors of a migraine headache and may constitute the aura of a convulsion resulting from disease of the temporal or occipital lobe Deafness, especially unilateral, of gradual onset associated with tinnitus and vertigo should call attention to the possibility of an acoustic neuroma or cerebellopontine angle tumor Of course what the patient calls dizziness often is not a vertigo but a peculiar sensation of floating or sinking, unsteadiness, or blurring of vision and need not be related to the eighth nerve

Weakness in mastication may be the earliest sign of myasthenia gravis, or difficulty in chewing may be the result of defective movement of the tongue and be an early sign of disease of the medulla, bulbar palsy, amyotrophic lateral sclerosis or syringomyelia It may also occur in the myopathies and progressive muscular atrophy Defective swallowing may be the result of disease of the medulla or of myasthenia gravis, and often it is the consequence of postdiphtheritic paralysis, occasionally it occurs in other polyneuritides, or in pseudobulbar palsy which may be the result of bilateral, at times trivial, strokes, or of polioencephalitis Pain produced by swallowing, often described by the patient as difficulty in swallowing, should call attention to the possibility of glossopharyngeal or trifacial neuralgia, or rarely, of multiple sclerosis or syringomyelia Hydrophobia and spasms of the muscles of deglutition of course occur in rabies, and trismus is commonly seen in tetanus Peculiar tic-like movements of the jaws and tongue are seen in the dystonias following encephalitis lethargica Attacks of smacking

the lips are manifestations of epilepsy and are associated with some modifications of consciousness

Dysarthria, frequently attributed to faulty fitting dentures or edentation, should call attention to the possibility of paresis, multiple sclerosis, disease of the medulla, Friedreich's ataxia, it also occurs, of course, in vascular accidents of the brain. Defects in phonation, with paresis of the vocal cords, are seen in tabes dorsalis and in disease of the medulla. When associated with dysphagia and nasal speech they may be a part of the picture of involvement of the vagospinal nerves from metastatic growths, or due to a lesion of the pons resulting from thrombosis of the posterior-inferior cerebellar artery. Spasm of the glottis in children results from tetany, and in adults is due most commonly to the laryngeal crisis of tabes but is seen also in rabies and in tetanus. Stertorous respiration, Cheyne-Stokes' respiration, Biot's respiration are found in the comas due to disease of the nervous system such as the apoplexies, brain tumor, abscess, meningitis, and likewise appear in general disease such as uremia, diabetic coma, the toxemias of pregnancy, etc. Dyspnea occurs in labio-glosso-laryngeal paralysis, in bulbar palsies, including the bulbar type of anterior poliomyelitis, in polyneuritis, in myasthenia gravis and in the myopathies, in paralysis of the phrenic nerves as in cord tumor or myelitis, and in paralysis of the intercostal nerves in similar disease and in anterior poliomyelitis.

Attacks of hyperpnea, frequently associated with dystonic movements and trance-like states, occur as the result of encephalitis lethargica, and respiratory spasms occur in that disease and in tabes. Slow respiration occurs at times as an evidence of increased intracranial pressure and in the state of hibernation produced by tumors of the pituitary gland. Hiccough is seen in bulbar disease, at times in anterior poliomyelitis, in myelitis, and particularly in some forms of epidemic encephalitis.

Among the disturbances of the function of the heart, palpitation may be observed in disease of the medulla and in epilepsy. Symptomatic tachycardia may be seen in lesions of the pneumogastric nerve in mediastinal disease, in diseases of the structures of the neck, such as abscess or tumor, in tabes, and in alcoholic and diphtheritic polyneuritis. In labio-glosso-laryngeal paralysis, acute bulbar palsy, Landry's paralysis, acute anterior poliomyelitis and amyotrophic lateral sclerosis tachycardia is often observed. Bradycardia is characteristic of conditions producing increased intracranial pressure such as meningitis. It is seen occasionally in dementia paralytica, in multiple sclerosis and in melancholia. At times it is associated with the state of hibernation due to pituitary disease. Increase of general blood pressure may be seen as a consequence of increased intracranial pressure following trauma, and in tumors, and may also be found in cases of pituitary basophilism, while a low blood pressure may at times be seen in epilepsy and pituitary hibernation. Among the vascular signs, cutaneous hemorrhage occurs in anterior poliomyelitis, in meningitis, and at times in myelitis, in multiple sclerosis and in purpuric myelitis. Alternating pallor and flushing

are often seen in meningitis and especially in the tuberculous form of this disease. Vasomotor disturbances are frequently observed in bulbar lesions, with or without hemianesthesia. Dermographism is common in the meningitides, and in Quincke's edema. In the peripheral neuritides erythematous and exfoliative dermatitis may be observed. Raynaud's disease may be mentioned as producing local asphyxia and gangrene, and intense rubor of the skin is observed in erythromelalgia. Severe trophic disturbances, with gangrene and atrophy, are seen in syringomyelia, in disease of the cauda equina and in spina bifida occulta. Edema is often seen in cerebral lesions, usually when there is an associated cardiac failure and it occurs in the hemiplegic side. It is also seen in transverse lesions of the spinal cord, in tabes, in syringomyelia, in paralysis agitans and in multiple neuritis. Other metabolic disturbances of the skin are the localized painful accumulations of fat in adiposis dolorosa, and the adiposity and purplish striations in pituitary basophilism. Chronic cyanosis is often seen in catatonic dementia praecox. Peripheral nerve lesions may result in cyanosis, erythema, glossy skin, keratosis, ulcerations and hypotrichosis. In lesions of the cerebrum and even more in those of the spinal cord decubitus ulcers and mal perforans are found. Anhidrosis is found in transverse lesions of the spinal cord, in paralysis of the cervical sympathetic and locally in lesions of the trigeminal nerve.

Many of the acute infections of the nervous system, such as meningitis, encephalitis and anterior poliomyelitis, are associated with constipation or at other times with diarrhea. Vomiting unassociated with the time of eating and often without nausea, projectile in character, sudden in onset, and at times occurring with headache and vertigo are characteristic of intracranial hypertension in tumors. At times what has been considered cyclic vomiting and acidosis of childhood has been found to be the result of a midline cerebellar tumor, producing few other localizing signs. Vomiting frequently occurs in lesions of the cervical spinal cord, occasionally in myelitis and often in the form of crises in tabes. In tabes also enteric crises with pain and constipation occur. Diarrhea is sometimes observed in tabes, although constipation, at times with tenesmus, is the rule. In transverse lesions of the cord constipation is found and in tabes and lesions of the conus and cauda equina incontinence is frequent.

Glycosuria may be found in lesions of the upper cervical cord, and albuminuria in cerebral hemorrhage, in brain tumors and in meningeal hemorrhage. The renal crises of tabes simulate renal colic.

Derangement of the bladder function may be brought about from a lesion of any level of the spinal cord and from disease of the cauda equina. Among the diseases giving rise to such derangements mention may be made of the following: transverse lesions of the spinal cord due to myelitis or caused by compression from diseased vertebrae, or from tumors, etc., diffuse diseases, as multiple sclerosis, disease of the posterior roots and columns, as in tabes

dorsalis, syringomyelia, tumors of the cauda equina, root neuritis and spina bifida occulta

When the defects of function of the nervous system are pronounced the cause of a disturbance of bladder function may be apparent, but it not infrequently occurs that the earliest sign of some of these diseases is related to the function of the bladder. In diseases producing a transverse lesion above the level of the reflex arc of the bladder sphincter, difficulty in starting the urinary stream is noted and at times dribbling may appear. The function of the bladder is interfered with in almost every case of tabes dorsalis. At times in addition to difficulty in starting the stream there is a lessened desire to micturate for long periods of time. Incontinence is frequently observed, early in the disease limited to a small amount sometimes after voluntary urination. Attention should be drawn to the occurrence of crises in tabes. Clitoridean crises in the form of paroxysms of voluptuous sensations with vulvovaginal secretion have been noted. Renal crises with severe pain in the region of the bladder and kidneys, eventually accompanied by dysuria, may appear. At times lightning pains may have their seat in the bladder and perineum. Disagreeable sensations during urination, and frequent and imperative desire to urinate are often observed. Difficulty in completely emptying the bladder with retention of residual urine is common.

In general, multiple neuritis is not associated with bladder disturbances but in a number of instances such disturbances have been known to occur. Bladder disturbances are not characteristic of amyotrophic lateral sclerosis, the spinal atrophies or myopathies.

Lesions of the cauda equina and spina bifida occulta may result in either retention or incontinence of urine.

Disturbances of menstruation, irregularity, infrequency and cessation are often among the first signs of disease of the pituitary gland and its environs, occurring with sufficient frequency to merit careful consideration.

In disease of the spinal cord sexual impotence frequently occurs. It is often seen in tabes dorsalis, in transverse lesions of the cord, in multiple sclerosis, and in lesions of the conus and cauda equina. Changes in the joints of the type known as Charcot joints may be seen in tabes and syringomyelia, other arthropathies are found in hemiplegia and peripheral nerve lesions. Atrophy of bones occurs in peripheral nerve lesions, in anterior poliomyelitis, in the myopathies, syringomyelia, tabes and dementia paralytica. In the last named three diseases spontaneous fractures are common. Arrested development of bone follows the cerebral palsies and the spinal paralyses of childhood.

Among the diseases producing disorders of the nervous system infectious diseases are paramount. In children encephalitis, leading to mental deficiency, cerebral palsies and epilepsy, is not an uncommon complication of the exanthemata as measles and scarlet fever, and of whooping cough. Meningitis likewise occurs, more frequently as the result of tuberculosis, pneumonia and influenza, but occurs in other infections as well. Venous

sinus thrombosis of the pyogenic variety often results from general septicemia, especially of the puerperal variety, and as the result of adjacent inflammatory lesions in the sinuses and mastoids. In similar conditions brain abscess and meningitis may occur. Non-pyogenic venous sinus thrombosis occurs in cases of cachexia in nutritional disorders or other wasting diseases. Hemiplegia due to cerebral arterial hemorrhage, thrombosis or embolism is dependent upon underlying disease for its cause. Cardio-vascular renal disease with hypertension frequently occasions cerebral hemorrhage, syphilitic arterial disease in the brain often leads to thrombosis, in active endocarditis and in bronchiectasis with local thrombophlebitis emboli are readily detached which may lodge in the brain. Diseases of the blood, as polycythemia, are often the causes of cerebral hemorrhage, and of thrombosis of cerebral vessels. Chorea is usually due to the rheumatic infection with accompanying endocarditis. Another type of chorea may be associated with pregnancy.

Degeneration of the spinal cord, as in combined degeneration of the spinal cord, is most frequently associated with pernicious anemia. Often the blood picture shows only a macrocytosis without anemia, but an achlorhydria is constant. Dietary deficiency diseases, such as pellagra, likewise produce degeneration of the spinal cord, and lesions in the spinal cord and peripheral nerves are seen in diabetes. In leukemia, infiltrations of the cord and brain occur, and of course metastases in these tissues may arise from any malignant tumor. The peripheral nerves are often affected by a multiple neuritis in diphtheria—less frequently in other infectious diseases. Multiple neuritis is characteristic of one form of beri-beri, and occurs also in other deficiency diseases and in diabetes. Women in the puerperal period are peculiarly susceptible to its occurrence.

The importance of recognizing cerebral involvement in infectious diseases is emphasized by the frequency of cerebral edema and meningismus in all severe infections. Acute confusional and stuporous states are common. Delirium frequently occurs and evanescent hemiplegias and visual disturbances are frequently observed in uremia and eclamptic conditions. Often the underlying pathology of a state of delirium or confusion is unrecognized.

Of the greatest practical importance is the recognition and correct interpretation of those signs and symptoms which may occur alike in diseases which are primary in the nervous system and in those which are primary in other bodily structures.

Coma occurs often as the result of certain bodily diseases, such as uremia, eclampsia, diabetes and terminal states, and likewise in cerebral diseases, such as meningitis, encephalitis, hemorrhage, thrombosis, embolism, abscess, sinus thrombosis, and brain tumor. I would direct your attention to only one feature in the differential diagnosis, namely, hemiplegia. Although it is true that hemiplegia may occasionally be present in eclampsia and uremia, usually a hemiplegia calls attention to the existence of other brain lesions.

The coma may be so deep, however, that the hemiplegia may easily be unrecognized, unless carefully sought for. Usually the coma is not so deep but that pricking the face with a pin will produce some grimacing, and then, the one side will be seen to contract more efficaciously than the other. If the lids are open they are further open on the paretic side. The nasolabial fold is more shallow, and at times puffing of the paretic cheek is seen in expiration. When the arm is passively lifted, the forearm extended and so placed that when it is allowed to fall, it would fall upon the face, unless the coma is unusually deep the forearm is stopped in its fall by a voluntary contraction. It usually falls more slowly, and at times may be held extended. If paralyzed, it falls quickly without interruption. When the lower extremity is passively flexed at the knee and hip and released on the paralyzed side, it falls into external rotation and slides into extension. On the normal side it is often held in the midline for a time or slowly extended. When the foot is passively dorsal flexed, on the normal side a contraction occurs in the tibialis anticus. Even in the comatose state the deep reflexes may be increased on the paralyzed side, great care being exercised to compare the responses of the two sides, and often the abdominal, cremasteric and plantar reflexes are absent on that side. When the abdominal wall or chest wall is pricked with a pin the patient, if able, will reach toward the spot only with the normal hand. It is very important to remember that when the soles are pricked, movement of the leg does *not* mean that paralysis is not present, as this often is a reflex and frequently leads to a wrong diagnosis.

Convulsions occur in idiopathic epilepsy, in gross disease of the brain and as the result of intoxication in metabolic, toxic and infectious diseases. Very careful inquiry into the history is essential in making a differential diagnosis. Often it will be found that preceding attacks occurred, even years ago. Of particular importance are the occurrences of little attacks. Often these are of such short duration and mildness that their significance as petit mal attacks is overlooked. They may consist of flashes of apprehension, tightness in the throat, a lump in the throat, a gone feeling, a dizziness, a sense of dreaming, a hesitation in speech or a momentary cessation of activity. Often they produce so little disturbance that the patient attributes but little importance to them. At times they occur more frequently, just before or at meal time. Fortunately, most of them are of longer duration and are associated with changes in color, slight salivation, widening of the eyes and staring, so that others note the attacks.

Rarely one observes attacks of sudden, lightning-like movements of the shoulders and arms, as if shrugging and flinging the arms upward. This is an epilepsy. Occasionally terror-like attacks occur, in which the child may run to the mother, cling to her a few moments and then shamefacedly resume play.

Frequent stumbling without reason often calls attention to an epilepsy and in one form (cataplexy) a sudden loss of all muscular tone occurs with

the patient dropping down, and then immediately arising. Usually the attack is brought on by an emotion of risibility, surprise or pleasure. It is important to observe, however, that not all muscular twitching and tremors are convulsions. Hypoinsulinism with convulsions should not be treated as epilepsy.

Pain is one of the commonest symptoms of all disease. Headache, often a prominent symptom of intracranial disease, must be carefully studied, as it is often present in other disease and in functional states, as the neuroses. In the latter it is never a pain. Although it is described as excruciating, terrible and unbearable, it is always a sensation and never a pain. It is a tightness, a fullness, a throbbing, a trickling, a pressure, a bursting feeling. It is always made worse by mental effort and emotional disturbance. On the other hand, the pain of intracranial disease is a real pain. In brain tumor it is very severe, throbbing, bursting, and occurs often in attacks associated with vomiting. It is worse on coughing, sneezing and straining. Frequently it may be brought on and at times stopped by change of position of the head. In cerebellar disease it is frequently suboccipital and associated with a rigid neck. It occurs at any time of the day and unlike the pain of sinus disease, is not affected by weather. Neither, as occurs in indurative headache, is there tenderness of the scalp, except in subtentorial lesions. Pains in the extremities and trunk are often attributed to a so-called neuritis or neuralgia. Unless there is evidence of diminished function of the nerve supposed to be involved, as paresis, loss of sensation, or change of irritability to electrical stimuli, the condition is not a neuritis but a referred pain. In the upper extremity the pain may be attributable to an arthritis of the shoulder or of the cervical spine or to a subacromial bursitis or a cervical rib. In the lower extremities it is usually the result of an osteo-arthritis of the spine, or of sacro-iliac disease, hip joint disease, or disease in the pelvis. Here it may more frequently be found that the sciatic nerve is actually secondarily involved in the lesion as shown by absent Achilles jerks.

To bilateral sciatica special attention must be paid, as it is not infrequently the sign of a lesion of the cauda equina. The Achilles jerks will usually be absent and anesthesia be found over the buttocks and sacral region, and the spinal fluid is often yellow or rich in albumin and globulin. The pains are radiating, burning, excruciating and always worse at night.

What is true of neuritis is even more true of neuralgia. With the exception of glossopharyngeal and trifacial neuralgia, the other algias are always referred pains from underlying pathologic lesions. In contrast to the face pains called neuralgic due to such diseases as sinus infections, infections about the teeth, etc., the pain of trifacial neuralgia occurs in attacks of very short duration and is provoked by stimulating a "trigger zone," by touch, chewing, talking and swallowing.

Root pains due to spinal cord tumors, tabes dorsalis, or pachymeningitis, when they occur in areas usually the site of pain in biliary, renal and

appendiceal disease, should not lead to useless abdominal operations, and the pains produced by disease of the spine, by osteo-arthritis, osteomalacia and tuberculosis should not be interpreted as being produced by spinal cord lesions. In the former instance careful examination will elicit defects in motion, sensation and reflex activity and there will be a lack of evidence of intra-abdominal disease, in the latter no evidence of disease of the nervous system will be found.

Weakness may occur in diseases of other organs than the nervous system. Many times a diagnosis of infantile paralysis has been made during an epidemic, in children suffering from rickets and scurvy producing a pseudo-paralysis. It is important also to note that failure of movement because of pain is not a paralysis. Not infrequently an arm or leg has been said to be paralyzed when it was not moved only because of pain. A tuberculous hip joint has often led to this error.

In occlusion of the leg arteries, from arteriosclerosis or thromboangitis an intermittent halt or claudication occurs in which the patient after walking a short distance finds it less and less possible to move the legs and finally must rest for a time, before he is again able to resume as before. The characteristic position of the hands and feet in carpopedal spasm occurring in spasmophilia and tetany, as well as the increased irritability of nerves and muscles should differentiate this condition from paralysis. The asthenia due to Addison's disease should not be confused with myasthenia gravis. Certain forms of polyarthritis are associated with a degree of muscular atrophy and weakness simulating neurologic disease. Sensory loss and reaction of degeneration are always absent.

Pupillary inequality due to unilateral paralysis of the cervical sympathetics as the result of apical pleurisy or lesions in the neck should not be interpreted as an indication of disease of the central nervous system.

From this rather disjointed catalogue one may discern the inseparability of neurology from medicine and conclude only that the practice of medicine is the practice of neurology.

MACROCYTIC ANEMIA IN BANTI'S DISEASE *

By D O WRIGHT, *New Orleans, Louisiana*

AN enormous literature has accumulated since Banti first described the three-stage syndrome to which his name has become the eponym. In reviewing countless descriptions that have appeared throughout the years, one finds the almost universal, and at times dogmatic, statement that the accompanying anemia is of the normo- or microcytic type.

A case of Banti's disease which shifted while under observation from a microcytic hypochromic type of anemia to one that closely resembled pernicious anemia during remission, has emphasized the fallibility of this statement. The purpose of this communication is to call attention to and suggest a possible explanation for this very definite metamorphosis.

CASE REPORT

F B, a white male, aged 35, was first admitted to the ward October 9, 1933, complaining chiefly of universal pruritus. General malaise, lassitude and some slight loss of weight had been more or less progressive for at least a year. Two or three months before admission jaundice and pruritus made their appearance. His past and family histories revealed no relevant facts. He was a man of good development but only in a fair state of nutrition. He had a very slight icteric tinge to the sclerae. Blood pressure was 126 systolic and 80 diastolic, pulse 80, respiration 16, temperature 98°. The liver was palpable 2 or 3 cm below the costal margin. The spleen was enlarged and very firm, extending almost to the umbilicus. A gastrointestinal roentgen series failed to indicate any gastric lesion other than pressure due to the enlarged spleen. Blood chemical tests were within normal limits. The Wassermann test was negative. The fragility test was within normal limits. Urinalysis showed sp gr 1.022, trace of bile, occasional pus cell and hyaline cast. The blood picture at this time showed

| | |
|---------|------------------|
| RBC | 4,535,000 |
| WBC | 4,000 |
| Hgb | 65% |
| CI | 0.72 |
| M C V † | 68 cubic microns |

He was discharged 10 days after admission. During the following two or three months jaundice was absent, he gained 18 pounds and was feeling much better in general. In February 1934 he began to lose strength and weight rather rapidly. There was some swelling of the abdomen which varied from time to time and jaundice reappeared. He was re-admitted to the ward March 26, 1934, with moderate amount of free fluid in the abdomen. The liver had increased in size considerably and was quite hard. The spleen reached almost to the umbilicus. At this time the blood count, showing a definite change from a micro- to a macrocytic anemia, was as follows:

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† Mean Corpuscular Volume—Volume of packed red cells expressed in cubic centimeters per 1000 c.c. of blood, divided by the number of red cells expressed in millions per cu. mm., an index of the mean size of red cells, the normal being 75–85 cubic microns.¹

| | |
|-------|-------------|
| R B C | 4,665,000 * |
| W B C | 4,000 |
| Hgb | 103% |
| CI | 1.11 |
| M C V | 99 |

The fragility test was repeated and found to be normal. The van den Bergh test gave a direct and immediate positive. Splenectomy was performed March 17, 1934. A note was made at operation that "the spleen was over the midline and down to the umbilicus. The liver was congested (hobnail type). Free liver edge was moderately rounded. The vessels in the omentum were large and engorged." Microscopic diagnosis, "moderate hyperplasia of the pulp with diffuse fibrosis, chronic splenic tumor compatible with Banti's disease."

On discharge the patient was greatly improved. There was no further ascites. The blood count made immediately before discharge from the hospital showed no appreciable change from the count on admission.

REVIEW OF LITERATURE

The not infrequent appearance of a slight macrocytosis and a high color index with portal cirrhosis has been widely recognized. Wintrobe and Shumacker,² Van Duyn,³ Goldhamer,⁴ Schulten and Malamos⁵ have recently called attention to this interesting phenomenon. A review of the less recent literature is included in the article by Wintrobe and Shumacker. In a recent communication⁶ I reported the blood pictures of 12 cases of portal cirrhosis and reviewed the records of 41 additional cases. The name pernicioïd (pernicious-like anemia) was suggested for this interesting condition. This descriptive term will be used in the discussion that follows.

Twenty-seven and four-tenths per cent of the 41 case records of portal cirrhosis which I reviewed showed a color index of 1 or more, and 18 per cent of the cases reviewed by Van Duyn had a color index of more than unity. Since a portal cirrhosis characterized the end stage of Banti's disease it would not be too bold to anticipate a macrocytic blood picture if and when the portal cirrhosis has progressed sufficiently.

Hanrahan⁷ reported 35 cases of splenic anemia. If his cases with ascites as well as those diagnosed cirrhosis at autopsy or operation are considered to have cirrhosis, this forms a group of eight whose average color index is .89. Three of these patients, or 37.5 per cent, had a color index of more than 1. In the remaining 26 cases (one has been excluded), which were without definite evidence of cirrhosis, only 11.6 per cent had a color index of 1 or more. The average color index of this group was .68, as contrasted with the color index of .89 of the cirrhotic group. The following pertinent observation made by Hanrahan is quite interesting: "We have seen how the approach to the pernicious type of anemia is marked by increasingly poor prognosis." The case omitted was one that showed a normal blood picture except for a color index of more than 1 when observed 25 years after splenectomy.

* A series of subsequent blood counts showed no essential change from this count.

REPORT OF 37 CASE RECORDS

The Charity Hospital records have been reviewed in an endeavor to substantiate the hypothesis that a macrocytic anemia develops in Banti's disease when liver cirrhosis develops. Thirty-seven records of Banti's disease were reviewed. All cases showing a positive Wassermann or any other possible etiologic factor were excluded. Nearly all of these patients had applied for admission late in the course of their illness as evidenced by the fact that 22 had a demonstrable amount of free fluid in the abdominal cavity at some time during their stay in the ward. A diagnosis of Banti's disease with cirrhosis was made on three other patients at autopsy or operation, forming a group of 25 with definite evidence of portal cirrhosis. Sixty per cent of this group had a color index of 1 or more, the average for the group being 1.04. Only 25 per cent of the remaining cases, which did not have definite evidence of cirrhosis, showed a color index of 1 or more. The mean color index for this group was much higher than one would expect, it being 0.92. This can be explained by the fact that their histories had been of long duration. Seventy-five per cent of this group had suggestive indications of portal cirrhosis, namely a palpable liver or a history of hematemesis extending over a period of several years.

The average age for the entire group was 31.8.

Gastric analysis was recorded in eight cases. Four out of this eight showed an absence of free hydrochloric acid.

SUMMARY AND CONCLUSIONS

A case of a patient with Banti's disease is reported whose blood count showed a very definite change from a hypochromic microcytic type of anemia to a macrocytic type closely resembling pernicious anemia in the stage of remission.

A series of cases diagnosed as Banti's disease have been analyzed to show that a color index of greater than unity is much more frequent and the mean color index higher in the groups with evidence of portal cirrhosis than in those without this complication.

It is a well substantiated fact that a macrocytic type of anemia frequently occurs in portal cirrhosis. From this case report and from a study of a series of cases of Banti's disease it is obvious that a macrocytic (pernicioid) type of blood picture will appear when portal cirrhosis develops. The concept that Banti's disease is always accompanied by a microcytic type of anemia is erroneous.

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ALKALOSIS is a term applied to that condition of the acid-base balance of blood in which the concentration of the blood bicarbonate is above the normal level. It may be more broadly defined as an abnormal condition caused by the accumulation in the body of an excess of alkali or by the loss of acid. Alkalosis has been observed clinically in a number of conditions, but has, however, been most frequently encountered in cases of Sippy management or in cases with pyloric or upper intestinal obstruction accompanied by vomiting. It is not the purpose of this report to consider the subject of alkalosis as it applies to clinical medicine in a general way, but to present a number of cases of hypertensive and renal disease in which an alkalosis was encountered.

Nephritis with nitrogen retention has generally been considered to be associated with a progressive acidosis. Whitney¹ and Chace and Myers² were among the first to point this out. The latter workers observed that in fatal cases of chronic nephritis with marked nitrogen retention showed a metabolic acidosis sufficient in many instances to be the actual cause of death. The term acidosis is a term applied to conditions in which the bicarbonate concentration of the blood is lowered, it may arise from several causes, a reduction of the total base concentration of the blood or an increase of the acid.

An influx of acid into the blood may occur from an abnormal formation as in diabetes mellitus or from a decreased elimination as in chronic nephritis. As to the retained acid, various workers have ascribed considerable importance on the one hand to a retention of phosphate,³ and on the other hand to a retention of sulphate.⁴ Recently considerable attention has been given to a lowering of the plasma total base concentration.

About six years ago a study was begun with the object of observing the progressive changes of the acid-base balance of the blood in cases of hypertension and various types of renal disease. It was the aim in this study to measure the blood as early in the disease as possible and then to follow the changes until termination. One of the first cases observed, clinically, appeared to be in a condition of acidosis. The nitrogen retention was only slight and the blood pressure was markedly elevated. To our surprise the bicarbonate concentration of the blood was not lowered but was at the upper normal or even slightly above. Interest was immediately aroused as to whether this was an exceptional finding or that perhaps it occurred occasionally in cases showing relatively little nitrogen retention but having a marked elevation in blood pressure.

Read at the Chicago meeting of the American College of Physicians, April 18, 1934.
From the Department of Biochemistry, School of Medicine, Western Reserve University, Cleveland, and the Division of Medicine, St. Luke's Hospital, Cleveland.

To date an acid-base balance study of the blood has been made of some 90 cases showing hypertension and renal disease of different types. Forty-five of these were cases showing marked elevations in blood pressure with only relatively little nitrogen retention. It is in this group of cases that the finding was made, of a tendency to an elevation of the plasma pH and bicarbonate content, which at the same time was accompanied by a tendency towards a lowered plasma chloride concentration.

Table 1 presents data of the acid-base balance of the plasma of three somewhat typical cases showing marked nitrogen retention. Since the blood

TABLE I
The Acid-Base Balance of the Plasma in Renal Disease with Nitrogen Retention

| Case No | Date | Plasma | | | | | Urea Nitrogen |
|---------|----------|--------|-----------------|-------------|---------|------------|---------------|
| | | pH | CO ₂ | NaCl | Protein | Total Base | |
| | | | Vol % | Mg /100 c c | Gm % | m Eq | Mg /100 c c |
| 1 | 3/11/30 | 7.28 | 26.5 | 569 | 6.3 | 138.2 | 105 N P N |
| | 4/ 4/30 | 7.18 | 24.9 | 575 | 6.6 | 140.0 | 160 " " " |
| | 4/15/30 | 7.09 | 29.8 | 536 | 7.2 | 135.8 | |
| 2 | 3/24/30 | 7.41 | 37.7 | 582 | 6.6 | 137.8 | 170 " " " |
| | 3/31/30 | 7.23 | 38.7 | 556 | 7.1 | 138.7 | 169 " " " |
| | 4/15/30 | 7.19 | 34.7 | 535 | 7.4 | 138.8 | |
| | 4/28/30 | 7.29 | 27.4 | 522 | 7.0 | 143.6 | 240 " " " |
| 3 | 11/13/29 | 7.44 | 63.2 | 616 | 3.6 | 150.8 | 13 |
| | 3/31/30 | 7.43 | 60.0 | 606 | 4.2 | 143.4 | 12 |
| | 10/28/32 | 7.30 | 49.0 | 647 | 5.6 | | 25 |
| | 11/16/32 | 7.33 | 43.2 | 626 | 5.8 | 148.3 | 95 |
| | 12/28/32 | 7.37 | 38.6 | 616 | 5.6 | 152.0 | |
| | 1/ 6/33 | 7.30 | 30.4 | 576 | | 146.9 | 146 |
| | 1/20/33 | 7.28 | 32.4 | 488 | 6.0 | 146.7 | |

findings of these cases are more or less typical of renal disease with nitrogen retention the cases will not be reviewed in detail. Cases 1 and 2 were clinically chronic glomerulo-nephritis, with terminal uremia. Case 3 was early the nephrotic type of acute nephritis, and terminated, as was confirmed at post mortem, a chronic glomerulo-nephritis. It is observed that both the pH and CO₂ are lowered and at the same time the final blood shows a definite lowering of the plasma chloride. The total base also tends to be lowered. In Case 3 attention should be called to the marked loss of chloride which occurred at termination. The patient experienced considerable vomiting. In fact the nausea and vomiting were so severe that no food could be taken for several days at a time. With this marked loss in plasma chloride the bicarbonate did not increase, as occurs in the vomiting from pyloric obstruction, but remained lowered. It should also be observed in this case that when the blood urea became elevated the bicarbonate had a tendency to fall.

Table 2 shows, in contrast, the change of the acid-base balance which may be observed in patients with a marked elevation in blood pressure and relatively little nitrogen retention

TABLE II
The Acid-Base Balance in Cases of Persistent Hypertension

| Case No | Date | Plasma | | | | | Urea Nitrogen |
|---------|----------|--------|-------|-------------|---------|------------|----------------------|
| | | pH | CO | NaCl | Protein | Total Base | |
| | | | Vol % | Mg /100 c c | Gm % | m Eq | Mg /100 e e |
| 4 | 9/12/28 | 7.45 | 66.0 | 562 | 6.3 | 146 | 13 |
| | 2/ 7/29 | 7.54 | 69.1 | 521 | 6.4 | 140 | |
| | 2/15/29 | 7.54 | 84.6 | 497 | 6.0 | | |
| | 2/23/29 | 7.56 | 84.2 | 492 | 6.5 | | 64 N P N 39 " " " |
| | 3/ 1/29 | 7.54 | 79.4 | 492 | 6.4 | | |
| | 3/ 9/29 | 7.56 | 81.2 | 486 | 6.0 | 137 | |
| 5 | 9/19/28 | 7.39 | 60.5 | 596 | 5.6 | 156 | 23 |
| | 10/ 9/28 | 7.52 | 66.8 | 544 | 6.0 | 142 | |
| | 10/24/28 | 7.41 | 80.9 | 497 | 5.9 | 140 | |
| 6 | 2/13/30 | 7.56 | 72.7 | 550 | 6.1 | 142 | 30 N P N 32 |
| | 2/19/30 | 7.59 | 73.6 | 532 | 6.6 | | |
| | 3/14/30 | 7.54 | 69.4 | 532 | 6.7 | 140 | |

Case 4 T W, female, aged 38, housewife, was observed over approximately two and one-half years. Her chief complaints were headaches, accompanied by nausea and vomiting, throbbing in the head, numbness and tingling in extremities, progressive weight loss and nocturia. During the latter period of her illness vision was seriously impaired.

The salient physical and laboratory findings were slight cardiac enlargement, systolic blood pressure which varied from 180 to 260, and diastolic pressure from 130 to 160, the fundi of both eyes showed arteriosclerotic changes, the uterus was about the size of a grapefruit, firm and apparently fibroid in nature, the urine showed a trace of protein during the last year of observation with occasional hyaline and granular casts, serological studies of both blood and spinal fluid were negative, complete gastrointestinal roentgen-ray findings were negative.

During the latter part of this patient's illness her most distressing problems were headache and vomiting, from which it was almost impossible to afford any effective relief. Consequently weight loss was very marked. During the last week of life typical carpo-pedal spasm was observed. A period of stupor of about two days' duration preceded death. Clinical diagnosis: Malignant hypertension, alkalosis, and slight cardiac hypertrophy.

It is seen that the plasma pH and bicarbonate content are definitely elevated and at the same time the plasma chloride is markedly lowered. It is interesting that the urine remained acid despite the elevated bicarbonate of the blood.

Case 5 J A W, male, aged 24, bookkeeper, was first seen 7/17/28, at which time his chief complaints were headaches, periodic in nature, occasionally accompanied by nausea and vomiting, slight swelling of both ankles, spots before the eyes, and nocturia two or three times a night.

History revealed a severe scarlet fever four years previous, several attacks of acute tonsillitis, appendectomy in 1918 and tonsillectomy in 1922.

A period of hospitalization at this time resulted in the following findings, albuminuric retinitis, slight cardiac enlargement, slight edema of both ankles, systolic blood pressure varied between 232 and 190 and diastolic varied from 160 to 120. Modified Mosenthal test showed a practically fixed specific gravity at a low level. Variations in day specimens were between 1.010 and 1.014. The night quantity from 8 p.m. to 8 a.m. showed a volume of 995 c.c. and a specific gravity of 1.010. Urine analysis showed a trace of protein and numerous hyaline and finely granular casts, a few erythrocytes and a few leukocytes.

On 8/16/28, approximately a month after first examination, after a very severe headache, patient was taken with convulsions and for three days remained in a stuporous state. Blood pressure was 200 systolic, 120 diastolic at this time. With usual therapeutic measures, he gradually improved and was able to leave the hospital in three weeks. During this time the highest blood urea N observed was 28.5 mg. and creatinine was 4.1 mg. Phenolsulphonephthalein excretion was 32 per cent in two hours. The final acid-base study was made just two days before death. The patient became progressively weaker and died 10/26/28 in coma. Clinical diagnosis: Chronic glomerulo-nephritis, slight cardiac hypertrophy.

Here again, as with the following Case 6, the pH and CO_2 are elevated while the chloride is lowered.

Case 6 M. H., female, white, aged 46, housewife. Present illness was of six years' duration, during which time the main symptoms were severe and frequent headaches, frequency of urination day and night, and weight loss. At the time the patient came under our observation, which was 50 days before death, there was some shortness of breath and cough on exertion. With bed rest these symptoms largely disappeared. Three days before death, the patient lapsed into a comatose state, accompanied by Cheyne Stokes respiration. Death occurred in this condition on 3/28/30. Past history revealed no severe illnesses, nor operations, six pregnancies, one still birth, one child died at five years, four children living and well.

Physical examination revealed a well developed but poorly nourished white female. Heart was moderately enlarged in all diameters without clinical valvular disease. Lungs showed a small amount of basal moisture, bilateral, which cleared with bed rest. Liver was just palpated below costal margin, firm but slightly tender. Blood pressure varied from 270 to 228 systolic and 170 to 150 diastolic. Eye grounds showed marked sclerosis of retinal vessels. Laboratory findings: urine showed a heavy trace of protein and numerous hyaline and granular casts, an occasional red blood cell and leukocyte. Blood N P N was 30.4 and 31.8. No alkali was administered at any time during the period of observation. Blood chemical studies here reported were made 2/13/30, 2/19/30 and 3/14/30, the last observation just two weeks before death occurred. When the blood samples were taken, signs of cardiac failure were not present in an appreciable degree.

Final pathological diagnosis: Arteriolosclerosis of kidneys, spleen, pancreas and suprarenals. Nephrosclerosis, marked, with multiple small hemorrhagic infarctions and hemorrhagic arterionecrosis. Discrete endarteritis of pancreatic arterioles with focal necrosis. Hypertrophy and dilation of heart. Multiple small anemic infarctions of myocardium. Multiple mural thrombi of both ventricles and right auricle. Multiple hemorrhagic infarctions of both lungs. Chronic passive congestion of liver, spleen and small intestine. Kidneys together weighed 226 grams.

To date we have observed about 12 such cases, wherein similar results were obtained. Of course the elevation of bicarbonate in all instances was not as great as in Case 4, however all of these 12 showed the blood bicarbonate concentration to be at the upper normal or above.

It has been our experience that it is a rather common procedure among

practicing physicians to recommend the administration of alkalis to patients with renal disease showing some clinical signs of an existing acidosis and to employ the reaction of the urine as a guide to therapy. It should be emphasized at the outset that the promiscuous use of alkalis in such cases is in certain instances irrational. That is, some cases are apparently not able to handle excess alkali as well as others. This observation is of course not new. In 1917, Palmer and Van Slyke⁶ showed that in normal individuals the urine changes alkaline after the administration of bicarbonate when the plasma CO_2 reaches 71 ± 5 vol per cent. It was pointed out by them, however, that in pathological cases this level of bicarbonate is not so well defined, and there is a danger of giving unnecessary and perhaps injurious amounts of bicarbonate if continued until the urine turns alkaline. Myers and Booher⁷ have reported two cases in which the urine remained strongly acid despite the development of an alkalosis. It is interesting that Case 4 excreted an acid urine despite the markedly elevated blood bicarbonate concentration.

Recently two cases have come under our observation which had been receiving alkali and in whom a definite alkalosis existed. Table 3 presents the observations on these two cases.

TABLE III
The Acid Base Balance of the Plasma in Renal Disease

| Case No | Date | Plasma | | | | | Urea Nitrogen |
|---------|---------|--------|---------------|-------------|-------------|------------|---------------|
| | | pH | CO_2 | NaCl | Protein | Total Base | |
| | | | Vol % | Mg /100 c c | Gm /100 c c | m Eq | Mg /100 c c |
| 7 | 2/29/32 | 7.50 | 77.5 | 529 | 6.3 | 159.0 | |
| | 3/ 1/32 | 7.47 | 87.6 | | | | |
| | 3/ 8/32 | 7.50 | 68.1 | 548 | 6.7 | 154.0 | |
| | 3/18/32 | 7.39 | 47.5 | 570 | 6.7 | 146.0 | 182 |
| | 3/25/32 | 7.17 | 27.2 | 575 | 7.4 | 154.0 | 150 |
| 8 | 3/ 8/33 | 7.50 | 87.5 | 502 | 6.9 | 166.0 | |
| | 4/24/33 | 7.46 | 74.5 | 533 | 8.2 | | |
| | 5/13/33 | 7.46 | 68.6 | 580 | 8.1 | 151.0 | 35 N P N |
| | 7/14/33 | 7.44 | 61.0 | 566 | 7.3 | 147.0 | 35 " " " |
| | 2/ 1/34 | 7.46 | 68.4 | 562 | 7.0 | | |

Case 7. C. T. male, white, age 42, was admitted to the hospital February 26, 1932, died March 26, 1932. Subsequent to his war experience in 1918, at which time he developed bacillary dysentery, he suffered from severe constipation and spastic colitis. Four years previous, following operation for hemorrhoids, he had an acute cystitis, proctitis, colitis and prostatic abscess. The latter ruptured into the rectum with sinus formation. Shortly after, he showed protein and formed elements in the urine and was considered to have an ascending pyelonephritis. Known hypertension existed for two years, and one year before, there was complete right hemiplegia. His chief complaints were severe throbbing headaches, nausea and vomiting, con-

stipation, frequency and burning on urination, progressive weakness and 58 pounds weight loss during the last year. In Dec 1931 he visited the Mayo Clinic and Dr Norman Keith kindly sent the following report of their findings: "He registered at the Clinic on December 16, 1931, and at that time we felt that he had a serious form of general arterial hypertensive disease. In addition to having the picture of so-called malignant hypertension in the eye grounds, there was some evidence of mild renal insufficiency. There was some myocardial degeneration, but no actual decompensation at that time. The urologic examination revealed a moderate amount of chronic, non-specific prostatitis which is probably secondary to the colon bacillus, the urinary culture yielded the colon bacillus."

Physical examination on admission to the hospital revealed a pale, markedly emaciated white male, with slight dyspnea. Weakness of right facial and orbital muscles was evident. Heart was enlarged 2 cm to left of mid-clavicular line. Lungs were clear, liver and spleen not palpable. Peripheral vessels were markedly sclerosed. Blood pressure was 240 systolic and 165 diastolic. Red blood cells 3,180,000, white blood cells 8,600, hemoglobin 65 per cent. Urine analysis: specific gravity 1.010, protein in moderate amount, a few casts, many leukocytes and a few red blood cells, phenolsulphonephthalein output February 29 showed 15 per cent the first hour and 20 per cent the second, total of 35 per cent in two hours. Standard urea clearance February 2—14 per cent, February 5—12 per cent of normal.

Hospital management: Alkaline ash diet was ordered on February 27. On March 3 diet was changed to one of low protein. Triple bromide, grains 15, was ordered on February 28 and the patient had received 10 of these tablets prior to our first blood chemical study on February 29. These were continued to March 5. Beginning March 3, ammonium chloride grains 10, three times daily, was given for a brief period to counteract alkalosis. On March 19 patient was transfused to which he reacted poorly, and developed acidosis, lapsed into coma and died in a uremic state.

Case 8 R. W., male, white, age 14, has been observed from 2/27/33 to date. He was hospitalized from 2/27/33 to 3/16/33 at which time the following history and findings were obtained. Five days before admission to hospital, onset of acute symptoms of present illness occurred, which were headache, backache, indigestion, and finally just before hospitalization a generalized convulsion. Past illness included measles, whooping cough and chicken pox. Previous to onset of present illness there was a history of nocturia and daily frequency, and a 10 pound weight loss during the last year.

Physical examination revealed an undernourished boy in a stuporous state. Heart was slightly enlarged and showed a pericardial friction rub. The blood-pressure was 176 systolic and 140 diastolic. Temperature varied from 37.5° C to 38.8° during the 18 days of hospitalization. The urine showed a trace to heavy trace of protein, occasional granular cast and an occasional red blood cell and leukocyte. Blood count: red blood cells 3,950,000, white blood cells 15,500. Blood urea N 25.8. Creatinine 1.6.

For a period of 10 days preceding the first acid-base study 8 gm of citrocarbonate were given three or four times a day upon the clinical assumption that the picture was one of acidosis. Subsequent acid-base studies were made without the exhibition of any alkali.

Diagnosis: Acute exacerbation of chronic glomerulo-nephritis.

During the past year there has been some gain in weight and some clinical improvement. Blood pressure, however, has persisted high, in January 1934 it was 190 systolic and 145 diastolic.

It is observed from table 3 that the pH and plasma bicarbonate content were markedly elevated at the time of the first observation. The chloride

concentration on the other hand was definitely lowered. Case 7 was given ammonium chloride for a short period. During this period the bicarbonate was decreased and the chloride was increased somewhat. As stated in the case review, he was transfused and reacted poorly. The terminal blood showed an uncompensated acidosis. Case 8 received no ammonium chloride. The alkalis were discontinued and a moderate amount of salt was given in his diet. The pH and CO_2 fell to within the normal range and the chloride increased to a lower normal value.

In conclusion we feel justified in stating that cases of hypertension and renal disease presenting a markedly elevated blood pressure with only slight, if any, increase in the blood non-protein nitrogen constituents, may show a shift in the acid-base balance of the blood, which is characterized by a tendency toward an elevated pH and bicarbonate content and a lowered chloride content.

The administration of alkali should be gauged by analyses of the plasma CO_2 , since apparently some cases are not able to handle excess alkali as well as others, and further since the distinction between acidosis and alkalosis clinically is in some cases rather hard to make. The promiscuous administration of alkali should be discouraged unless carefully controlled by blood acid-base analyses.

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OBSERVATIONS OF REMISSIONS IN HYPERTHYROIDISM INDUCED BY PREGNANCY URINE EXTRACT[†]

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Two years ago the administration of pregnancy urine extract (Antuitrin S) † to patients with hyperthyroidism was begun in this Clinic ‡. A summary of metabolic results has been reported¹. In some patients a rapid remission occurred. The thyroid status of these patients a year or more later is to be given in this paper together with brief clinical descriptions. Six new case reports are presented. The characteristics of those patients in whom remission was not induced will be analyzed. The 13 patients are divided into four groups. Treatment consisted of one cubic centimeter of Antuitrin S (100 R U) or of Theelin (50 R U) given subcutaneously daily or three times a week for specified periods before or after menses as indicated. Antuitrin S is referred to as P U E.

GROUP I

Three patients of a type now thought to be unsuitable for pregnancy urine extract treatment were observed during the summer and fall of 1932. The results in these patients have been reported. The group is composed of two older women and a boy of 17 years.

Case 1 A woman, Mrs G M, 53 years old, whose last menses had occurred two years before, was admitted to the Clinic in August 1932. She had lost 39 pounds in the last five years, during which time she had been nervous and easily excited.

On examination the pulse rate was 112, regular, she had a moderately enlarged, firm goiter. The basal metabolic rate in August 1932, was +30 per cent. She was given P U E and Theelin alternately, daily for three months. During this time no menstruation occurred and the basal metabolic rate was not significantly altered. The final reading, before operative treatment in December 1932, was again +30 per cent.

Case 2 Mrs L S, 46 years old, had had a goiter for 23 years. She was still menstruating regularly. She had been conscious of palpitation and increasing nervousness for two years.

On examination a vascular hypertension (190-100), a nodular goiter and a fine tremor of the hands were found, but no exophthalmos. Before treatment the basal metabolic rate was +39 per cent and +37 per cent on two occasions. P U E was given after the menses in October, followed by Theelin for two weeks, and P U E again three times a week during the month of November. Menstruation in November was delayed. Following a temporary drop, a rise in metabolic rate occurred during January and February, the fourth and fifth months of observation. Following the menses in January, P U E was given daily for two weeks and the metabolism rose to +53 per cent. Operative treatment was then successfully carried out.

Case 3 E A, a boy 17 years old, whose mother had had hyperthyroidism, came

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† Generously furnished by Dr E A Sharp, Parke, Davis & Company.

‡ From the Thyroid Clinic, Northwestern University Medical School, Chicago.

to the clinic in November 1932. He had developed a typical exophthalmic goiter following an upper respiratory infection six months before admission.

On examination he had slight exophthalmos, tremor, weakness, and a small, diffuse goiter. The pulse rate was only 84. The basal metabolic rate was $+36$, $+39$ and $+54$ per cent on successive determinations before treatment. He was given P U E three times a week for five months. After the first month of treatment a transient remission occurred (basal metabolic rate $+11$ per cent). This was soon followed by a recurrence, at the end of treatment the metabolic rate was $+26$ per cent. There had been a 10 pound gain in weight but clinically no diminution of the hyperthyroidism had occurred.

GROUP II

Two very mild cases were first treated in the spring and summer of 1932.

Case 4 A thin, nervous girl of 19 years, whose mother has a goiter, was examined in April 1932. Goiter was first noted at 14 years of age. She had been nervous for three years, had always been thin, had lost from 108 to 103 pounds, she had never had cardiac palpitation until three months before examination. She felt warm, perspired freely, had noted weakness and shakiness of her legs. The menses had been irregular, occurring at intervals of from six weeks to two months. Amenorrhea for four months had occurred once. She had bilateral headache before menses. This history suggested hyperthyroidism with failure of ovarian function to become predominant in the third phase of puberty.

Examination found a thin, easily excited girl with considerable symmetrical goiter, pulse 140, bright eyes without definite exophthalmos, and a fine tremor. The heart and lungs were normal. Four basal metabolic rates during a control period of seven weeks were $+19$, $+15$, $+10$ and $+16$ per cent. The average weight was 99 pounds, pulse average 108.

Treatment was started 26 days after the preceding menstrual period, it consisted of eight injections of P U E given in a period of 15 days. Menstruation occurred after the first two doses. Injections were continued through and for eight days after menses.

Result The three basal metabolic rates during a six week period immediately following this 15 day course of injections were -6 , -4 , and -14 per cent, with weight rising to 103 pounds and pulse averaging 82.

Subsequent observations from August 1932 to December 1933, 18 months from treatment, found a basal metabolic rate average of -8.5 per cent, with weight range from 101.5 to 104.5 pounds, and pulse range from 72 to 96. Menstruation occurs regularly every 30 days and lasts four days. The goiter is diffuse and somewhat smaller. Her nervous temperament seems about the same but thyrotoxic symptoms of tremor, tachycardia and muscular weakness are absent.

Case 5 A Polish woman, 33 years of age, whose youngest child was a year old, reported to the clinic in August 1932. She complained of nervousness, weakness, palpitation and tremor. On examination there were no exophthalmic signs but marked tremor and a diffuse, small goiter without bruit were found. The basal metabolic rate was $+29$ per cent, pulse 90, weight 110 pounds.

Treatment One cubic centimeter of P U E was given subcutaneously three times a week for eight weeks. During treatment two regular menstrual periods occurred, three basal metabolic rates during this time averaged $+19$ per cent. Two weeks following treatment the metabolic rate was $+13$ per cent, after four weeks it was $+6$ per cent, and for five months ranged from $+5$ to -8 per cent, she gained eight pounds in weight and the pulse rate dropped from 90 to 76. Clinically she became non-toxic and undertook factory work.

Two moderately severe cases of hyperthyroidism in young women were then treated

Case 6 An unmarried Italian immigrant girl, 17 years of age, was admitted to the clinic in September 1932. She had come to Chicago when she was seven years of age. A goiter was noted three years later. She complained, on admission, of weakness, nervousness, excessive sweating, difficulty in climbing stairs due to weakness of her legs, and slight loss of weight. She stated that menses of four days' duration occurred every 28 days.

On examination the pulse was regular, very fast, 144, there were marked tremor, excessive sweating, no exophthalmic eye signs, a small, smooth, symmetrical goiter. Two basal metabolic rates before treatment were $+67$ and $+34$, per cent, weight average 120 pounds, pulse average 118.

Treatment was given for seven weeks from September 16 to November 7, 1932, consisting of P U E given for one week after three successive menses, and Theelin given for two weeks preceding the second and third menses.

The result of treatment in this case was extremely dramatic in contrast to the preceding and subsequent cases. The metabolic rate during the seven weeks' treatment progressively dropped to $+3$ per cent, the weight increased 20 pounds, the pulse dropped to 96. Clinical signs of toxicity disappeared. She seemed phlegmatic.

Subsequent observations have found her in a steady state as regards basal metabolism. Tests during 13 months' observation have been -2 , ± 0 , -4 , and -4 per cent, weight average 139 pounds, pulse from 72 to 88. She is doing factory work. The goiter which was not large at any time seems unchanged by gross clinical observation.

Case 7 A married German girl of 22 years entered the clinic on January 5, 1933. She had delivered her first child in May 1931, eight months later, in January 1932, she noted a goiter and she became extremely irritable. Separation from her husband occurred at this time. She lost 36 pounds in weight. Partial recovery from this apparent acute hyperthyroidism occurred during 1932, evidenced by gain in weight, but she still complained of nervousness, irritability and weakness.

On examination the pulse was 110, there were marked tremor, slight sweating, slight definite exophthalmos, a soft, diffuse pulsating goiter giving a bruit. The basal metabolic rates for three weeks in January 1933, before treatment, were $+34$, $+53$, and $+49$ per cent, pulse average 138, weight 136 pounds.

Treatment was given for one week before the menses in February and March 1933. One week after menstruation in March the metabolic rate was $+15$ per cent, pulse 96, weight 142 pounds. This sudden remission, similar to that in Case 6, was, however, not maintained and in April the metabolic rate rose to $+33$ per cent. P U E had been given in March and after the menses in April. Subsequently, however, with further administration of P U E during May and June, the basal metabolic rate dropped to $+2$ per cent in July 1933, and since then for nine months the patient has been in a steady metabolic state with readings of $+7$, $+6$, ± 0 , $+5$ per cent, and in April 1934, -10 per cent. For six months she has been working hard and long as a general housemaid.

GROUP III

In contrast to these four very successfully treated patients, three succeeding patients were not benefited. These have not yet been reported.

Case 8 Mrs. M. P., 34 years of age, entered and lost 48 pounds in weight, from 198 to 150 pounds.

On examination the pulse was 108, there were marked tremor no exophthalmic signs, a smooth soft goiter without bruit The basal metabolic rates before treatment were +58, +44 and +41 per cent, pulse 108, weight 150 pounds

P U E given before menses in February and March led to a drop in metabolic rate to +16 per cent, with a pulse of 76, weight 156 pounds This marked remission, however, was not maintained During April an upper respiratory infection occurred and in spite of two further courses of P U E the metabolic rate rose to +57, +53 and +56 per cent

Case 9 Mrs M M, 30 years of age, presented herself at the clinic on May 23, 1933 She had had a pelvic infection after marriage at 17 years of age, and had had two pelvic operations at 23 and 24 years, in one of which the right ovary had been removed Menses, since these operations, had been regular but of only one day duration Her complaint was of fatigue, tachycardia, sweating, occasional diarrhea, and loss of 15 pounds in weight

On examination the pulse rate was 120, she had a fine tremor, and a small thyroid enlargement on the right, with no other definite signs The basal metabolic rates during three weeks of observation were +44, +36 and +40 per cent, average weight 141 pounds, pulse average 108 P U E was given for three weeks after menses, Theelin for one week before the next menstrual period, and P U E again for 12 days after it During this month the basal metabolic rate rose to +53 and +55 per cent Not even the temporary remission that had occurred in other unsuccessful cases was present in this Lugol's solution was then started and in turn failed to reduce the metabolic rate, but following thyroidectomy this determination was -8 per cent, and marked clinical improvement occurred

Case 10 M C a negress, 25 years of age, came to Chicago from Mississippi six years ago A year later she delivered a child which lived six months, two miscarriages occurred subsequently Her complaint was of blurring of vision, nervousness, marked loss of weight, and excessive weakness She presented on examination an ophthalmoplegia and such marked muscular weakness as to suggest myasthenia gravis The thyroid was considerably enlarged, tense, not nodular, and had no bruit The basal metabolic rate was +50 and +51 per cent, weight average 138 pounds, pulse rate average 114

Theelin and P U E were given for three months with no effect on the metabolic rate

GROUP IV

The three cases in this group are still under observation They have had marked clinical improvement but are not entirely free of hyperthyroidism as indicated by the basal metabolic rate

Case 11 A married woman (Mrs L O'R), 41 years of age, reported to the Clinic on July 11, 1933 For two years she had had nervousness, tremor, sweating increased appetite and emotional irritability Her menses had usually been of three days' duration but had been decreasing and had been absent for four months She had never had a goiter

On examination she was found to have a very marked tremor, slight failure of convergence of the eyes, a slight enlargement of the thyroid, and a pulse of 120 Two metabolic rate tests during a three weeks' control period were +65 and +50 per cent, with pulse average of 118, and weight average of 124 pounds

Treatment, in the absence of menses, was begun with Theelin, 1 cc every other day for four weeks Menses occurred and P U E was given three times a week following this period for two weeks The basal metabolic rate at the end of this time was +23 per cent, pulse 115, and weight 127 pounds For the next three

months Theelin and P U E were used alternately. Another irregular menstrual period occurred. Following this the basal metabolic rate was $+10$ per cent, pulse 83, weight 131 pounds. A clinical cure seemed in progress, but during the next four months, although the weight has steadily increased to 140 pounds, a gain of 16 pounds, and has been maintained, the basal metabolic rate has risen to an average of $+25$ per cent, and the pulse to 100. No menses have now occurred for three months.

Case 12 A married woman of 38 years (Mrs W B) came under observation on December 11, 1933. Her complaint was that for four months she had had marked weakness, tremor, nervousness and sweating. Three day menses were at a 23 day interval.

On examination she appeared exceedingly thyrotoxic. There was very marked tremor, extreme quadriceps weakness, a regular pulse of 130, no definite exophthalmos, and a diffuse, firm goiter without a bruit. Three metabolic rate measurements before treatment were $+61$, $+58$, and $+51$ per cent, with average weight of 107.5 pounds, and average pulse of 122.

P U E was given daily for three weeks, then for one month. P U E and Theelin were given alternately daily, after the second menses during treatment. P U E was given daily for eight days. During this course of treatment there was no definite improvement although the metabolic rate declined to $+40$ per cent, the pulse average to 118, and the weight decreased to 105. The next menstrual period was delayed two weeks. A normal flow then occurred. At this time a definite transition toward recovery began. The weight began to rise steadily, muscular strength increased, the pulse rate and metabolic rate dropped progressively. The last metabolic rate, after five months of treatment, was $+15$ per cent, pulse 86, weight 118 pounds—a gain of 13 pounds. P U E has been given after each of the last three menses occurring since the delayed flow in February. The patient is now doing her own sewing and other housework, and feels in nearly normal health. This is the most severely thyrotoxic patient we have treated.

Case 13 Mrs L P, 35 years of age, married, of Russian nationality, was admitted to the clinic on October 4, 1933. Her second marriage (of four years' duration) was a happy one. There have been no pregnancies. Dr B F Heskett reported an infantile uterus. Her complaint was of fatigue, cardiac consciousness, nervousness and tremor. She had been 25 pounds below her normal weight for several years, and she had many headaches, some of which occurred premenstrually.

On examination she appeared thin but quiet. The pulse was 98. There was no exophthalmos, but a fine tremor and a diffuse goiter were present. The basal metabolic rate before treatment was $+35$ and $+42$ per cent, with a pulse of 96, and weight average 108 pounds.

P U E was given for one week after and Theelin for one week before succeeding menses. The metabolic rate dropped to $+23$ per cent. P U E was then given daily for five weeks during which a regular and an early menstrual period occurred. Toward the end of this course the metabolic rate rose sharply to $+45$ per cent. No menses then occurred for five weeks and with the return of regular menses, as in Case 9, a distinct transition toward recovery took place. Weekly metabolic rate readings dropped rapidly in nine weeks to $+2$ per cent, with a pulse of 68, and weight 116 pounds—a gain of 8 pounds. The last observation four months later is $+10$ per cent, pulse 76, weight 111 pounds. The patient states that she is doing her usual amount of housework.

SUMMARY

Thirteen cases of hyperthyroidism have been treated with pregnancy urine extract and Theelin (see table 1). The usual course of treatment

TABLE I

| | Age | Apparent Ovarian Function | Average B M R before Rx | Duration of Treatment | B M R after Rx | Comment |
|--------------------|-----|---------------------------------|----------------------------------|-----------------------------|----------------------|--|
| <i>Group I</i> | | | | | | |
| Case 1, Mrs M | 53 | Menopause | +30 | 3 months | +30 | Postmenopause Goiter, 23 years Hypertension Male |
| Case 2, Mrs S | 46 | Regular | +38 | 5 months | +57 | |
| Case 3, Mr E A | 17 | — | +43 | 5 months | +26 | |
| <i>Group II</i> | | | | | | |
| Case 4, Miss V P | 19 | Irregular | +15 | ½ month | — 3 | B M R—8% 18 months later |
| Case 5, Mrs M | 33 | Normal | +29 | 2 months | + 4 | B M R—4% 13 months later |
| Case 6, Miss G deF | 17 | Normal | +50 | 1½ months | — 2 | |
| Case 7, Mrs A W | 22 | Normal | +49 | 5 months | + 1 | B M R—10% 10 months later |
| <i>Group III</i> | | | | | | |
| Case 8, Mrs M P | 34 | Normal | +45 | 3 months | +55 | Initial success, in fection-failure Pelvic infection, ovariectomy Atypical myasthenic hyperthyroidism |
| Case 9, Mrs M M | 30 | Reduced | +40 | 1½ months | +54 | |
| Case 10, Mrs M C | 25 | Unknown | +50 | 3 months | +50 | |
| <i>Group IV</i> | | | | | | |
| Case 11, Mrs P R | 41 | Reduced | +57 | 7 months | +17 | Amenorrhea has occurred |
| Case 12, Mrs B | 38 | Normal | +56 | 5 months | +15 | Marked gain of weight and strength |
| Case 13, Mrs L T | 35 | Normal | +38 | 5 months | + 9 | Normal activity |

lasted for four or five months, the shortest was two weeks, the longest seven months. Remission of hyperthyroidism has occurred coincidental with this treatment in seven cases. The six failures are as follows: A boy, a woman two years past the menopause, a woman with hypertension and nodular goiter of 23 years' duration, who was at the menopause, a woman in whom remission had been induced, who experienced an upper respiratory infection, a woman of 34 years who had had two pelvic operations for infection and adhesions, in one of which the right ovary had been removed, and a negress with excessive, atypical myasthenic hyperthyroidism. The women in whom the treatment has been successful are definitely below the menopause, they have no history of ovarian disease. It would, therefore, seem that the induction of remission by pregnancy urine extract is dependent on normal ovarian function.

DISCUSSION

At the present time no physiological proof that the remission occurring in these cases may be attributed to the P U E, and Theelin treatment can be given because the mechanism of such an action is unknown. Nevertheless, remissions have occurred, abruptly in the healthiest adolescent girl,

TABLE II

| | | | |
|---------------------|---------|---------------|-------------------------------|
| Case 1—Total dosage | P U E | 45 cc | |
| | Theelin | 45 cc | |
| Case 2— | " | P U E 7 cc | } in October |
| | " | Theelin 14 cc | |
| | " | P U E 12 cc | |
| | " | P U E 14 cc | |
| Case 3— | " | P U E 60 cc | } in November |
| Case 4— | " | P U E 8 cc | |
| Case 5— | " | P U E 24 cc | } in January |
| Case 6— | " | P U E 9 cc | |
| | " | Theelin 12 cc | |
| Case 7— | " | P U E 4 cc | } in February |
| | " | 14 cc | |
| | " | 8 cc | |
| | " | 18 cc | |
| Case 8— | " | P U E 8 cc | } in May and June |
| | " | 8 cc | |
| | " | 10 cc | |
| | " | 6 cc | |
| Case 9— | " | P U E 15 cc | } after menses |
| | " | Theelin 7 cc | |
| | " | P U E 6 cc | |
| Case 10— | " | P U E 33 cc | } before menses |
| | " | Theelin 26 cc | |
| Case 11— | " | Theelin 15 cc | } after menses |
| | " | P U E 7 cc | |
| | " | Theelin 9 cc | |
| Case 12— | " | P U E 11 cc | } following menses |
| | " | P U E 21 cc | |
| | " | P U E 16 cc | |
| | " | Theelin 21 cc | |
| Case 13— | " | P U E 7 cc | } alternately |
| | " | P U E 4 cc | |
| | " | Theelin 4 cc | |
| | " | P U E 18 cc | } after each menstrual period |
| | " | | |
| | " | | } after menses |
| | " | | |
| | " | | } before menses |
| | " | | |
| | " | | } daily |
| | " | | |

and more gradually in the adult women. In two cases the return of menstruation, which had ceased during P U E treatment, was coincident with remission as evidenced by gain of weight, previously stationary, and reduction of metabolic rate to or nearly to the normal zone.

In attempting to explain this remission one might be led to assume that a suppression of pituitary function had occurred as a result of P U E administration. This would be beneficial if hyperthyroidism were due to excess of thyrotropic hormone from the anterior pituitary. This latter, an attractive hypothesis—hyperpituitary hyperthyroidism—while probable in some cases, has no evidence to support it. Indeed Aron² suggests just the opposite—that in hyperthyroidism, thyrotropic pituitary hormone production is reduced, while in hypothyroidism it is increased.

Largely as a result of the clinical observation that remission can not be produced in the absence of cyclic ovarian function, we are for the present using the working hypothesis that the pregnancy urine extract effect on hyperthyroidism is due to its action on the ovary. A small number of clinicians have reported the histologic change occurring in the human ovary after the administration of P U E. The work of Geist³ and Mandelstamm⁴ has previously been referred to. More recently Hamblen,⁵ using

Antuitrin S, has also found not luteinization but on the contrary, in nearly every case, multiple follicular retention cysts. He suggests that folliculin production may be increased. Collip's⁶ studies suggest that the universal effect of A. P. L. is not the formation of corpora lutea but an action on the theca interna. One might then suppose that the mechanism involved is as follows. A primary stimulation of Theelin secretion and circulation (as in Cases 4 and 6) or an early follicular retention of Theelin leading to delay or cessation (as in Cases 12 and 13) followed by a steady and heightened circulation of Theelin when administration of P. U. E. was discontinued. Riddle⁷ has demonstrated in ring-doves that in spring and summer when ovarian weight and reproductive activity are increased, thyroid weight and activity are decreased, but that the thyroid is hyperplastic during the 44 hour ovulation period in the pigeon. Sherwood, Savage and Hall⁸ found that daily injections of from 10 to 800 rat units of Amniotin lowered the metabolic rates of rabbits 37 per cent when these animals were also being given thyroid, and lowered the rates of rats 42 per cent below normal in oophorectomized animals and 20 per cent below normal in intact animals. The effect of theelin on thyroid activity has been studied by Aron⁹ who found that large doses of "folliculin" would prevent the thyroid hyperplasia of pituitary thyreotropic hormone. Kunde¹⁰ found the metabolism of normal adult female dogs to be slightly lowered by continuous administration of estrin with production of estrus. More recently Laprida¹¹ produced regression of thyroid activity in the rat by injections of "folliculin". We, therefore, assume that immediate or delayed increased Theelin secretion and circulation result from the pregnancy urine extract injections and that this increased level of Theelin in the blood stream inhibits the thyroid. We realize that this theory is at present purely speculative.

CONCLUSION

Remission of hyperthyroidism occurred in seven young women treated with pregnancy urine extract (Antuitrin S and Theelin). This remission has now continued for 18 months in the earliest successful case. No recurrence in others has been observed as yet. It is assumed from our experience that this effect may be the result of an action of the extract on the ovarian production of Theelin. From our experience in six other cases such treatment would not be productive of remission in women at or beyond the menopause or in those in whom interference with ovarian function by surgery or disease has occurred.

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THE INCIDENCE OF STREPTOCOCCAL INFECTION IN CARDIOVASCULAR SCLEROSIS [†]

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THERE is a form of cardiovascular disease, seen more frequently than that due to syphilis, which is characterized by dilatation of the aorta and large vessels and a gross enlargement of the heart without special valvular defects. Its clinical course resembles that of syphilis in that symptoms referable to congestive failure make their appearance usually in the fourth and fifth decades of life. When aortic regurgitation is absent in cardiac syphilis a differential diagnosis between the two forms of heart disease may be quite impossible to make during life, and indeed at times a pathological anatomic differentiation may be impossible without the recognition of spirochetes in the tissues. This form of heart disease is usually referred to generically as degenerative cardiovascular disease, atherosclerosis, atheromatosis, chronic myocarditis, or simply the arteriosclerotic heart. Albrecht ¹ (1906) referred to the associated dilatation of the aorta and large arteries as an idiopathic form of arteriosclerosis, and believed the mechanical factors of stress and strain, the local impinging of the blood stream upon the walls, to be the principal cause of it.

When congestive failure sets in, the clinical course of the patient suffering from this form of heart disease is, again like that of syphilis, as a rule, progressively down hill, a fair degree of recompensation, as seen with the rheumatic heart, does not follow treatment. The patient dies during his first period of failure or he lingers on, a complete invalid, for at most two or three years. Before the onset of failure, death frequently occurs from acute coronary occlusion or one of its sequelae, such as rupture of the heart wall. Sixty-five per cent of Benson and Hunter's ⁵ series of 200 cases of acute coronary occlusion belonged in this group of cardiopathies, the remaining 35 per cent were divided about equally between the syphilitic heart and the heart of senile arteriosclerosis. Likewise in their ⁶ series of 40 cases of rupture of the heart there was but one instance of proved syphilis, the remaining cases belonging to the group now under discussion.

It is agreed by all workers in the field of arteriosclerosis that the structural changes in the wall of this type of sclerotic artery are different from those of syphilis, from the medial lesions caused by adrenalin, and from those seen in the Monckeberg type of the disease. There is no agreement, however, as to the nature of the cause or causes of the type of sclerosis under discussion. It would seem that several factors may be concerned. The

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mechanical factor of stress and strain, and the changes incident to disturbed metabolism—with high protein and high fat intakes leading to deposition of cholesterol esters in the intima—have been considered the most probable causes^{1, 2} But, seemingly, investigators will not give up the idea that infection in some way plays a rôle in the pathogenesis³ By experiments on rabbits and dogs, the results of which are certainly not applicable to man in their entirety, and by the statistical studies of clinical cases and necropsy material, an effort has been made repeatedly to link infection with the disease Klotz (1912) from a study of the aortae and coronary arteries in 15 cases of acute rheumatism, states the arteries react to the irritant in a true inflammatory manner In the small arteries a nonsuppurative infiltration chiefly of lymphoid cells is seen in the adventitia and outer layers of the media In the larger vessels and the aorta the inflammation follows the vasovasorum The intima does not seem to be primarily affected, but later proliferates It is a picture of chronic productive mesoaortitis more like that of syphilis than true arteriosclerosis Boinet and Romary (1897) found streptococci in early arteriosclerosis of the aorta in a patient dead of erysipelas and in another dying of rheumatic pericarditis Ophul's very comprehensive study of necropsies from the standpoint of the relation of previous infections to the presence of arteriosclerosis found at autopsy led him to the conclusion that infections of the rheumatic type played an important role He states that the arterial lesions seemed to reach their full development after the active infectious process had long subsided In the seventh of the conclusions at the end of his monograph he says "The tissue changes in arteriosclerosis are partly inflammatory but to an equal extent degenerative and reparative In the arterioles the initial lesion seems to be a lateral subendothelial hyaline thrombosis followed by organization In larger arteries there is evidence of endothelial damage, permitting the entrance into the intima of blood plasma and blood cells followed by proliferation and degeneration"

Although the experimental evidence of the relation of infection to arteriosclerosis is suggestive and the statistical studies of necropsy material point the finger of suspicion to the same, MacCallum⁴ in a recent review of "Acute and Chronic Infections as Etiological Factors in Arteriosclerosis" concludes that "In spite of these experiments and the statistical studies of coexisting or later occurring arteriosclerotic lesions in persons affected with infectious diseases, there is no satisfactory proof of the thesis that infection is the direct cause of arteriosclerosis" Again, he summarizes the subject matter in general as follows It appears that there is but little evidence in favor of the idea that infections, whether acute or chronic, play a great part in the pathogenesis of arteriosclerosis In typhoid fever the lipid streaks may be a transitory phenomenon In tuberculosis, rheumatism, arthritis, *Streptococcus viridans* endocarditis and septicemia, and in glomerular nephritis from infections, there is no special tendency to the development of arteriosclerosis In diabetes mellitus, arteriosclerotic nephritis and cholelithiasis one finds arteriosclerosis in the majority of cases

With this background of confusion in mind the clinician is occasionally brought face to face with instances of congestive heart failure which can not be relieved by the usual methods and principles of therapy. He is then undoubtedly justified in such instances in searching for and removing, if possible, any disease which may have some bearing upon the irremediability of the condition in question. Actuated by these motives, we have collected in the past few years a small series of cases in which the cardiac conditions found present seemed to be related to the presence of chronic sinusitis, of chronic cholecystitis, and of severe grades of chronic pericemental dental infection. The coincidence of cholecystitis and heart disease has been noted several times by pathologists. Benson, Hunter and Manlove⁶ found cholelithiasis present in 17.5 per cent of their 40 cases of heart rupture. In only one instance of this series was the rupture due to a proved syphilis. The possible relationship between gall-bladder disease and heart disease has also been commented upon by clinicians.⁷ To us the group in which chronic hyperplastic sinusitis seemed to have some bearing has been of more interest, and we have studied the biopsy material and in one instance the heart removed at autopsy in the hope of finding suggestive evidence of an etiological relationship.

The following histories of some of the patients, briefly outlined, give the important clinical points in the series.

CASE REPORTS

Case 1 R. M. W., a business man, aged 59, entered the hospital (3/7/27) with cardiac failure on the basis of chronic cardiovascular sclerosis with hypertension. Under hospital control it was found impossible to restore compensation by the usual principles of treatment. Orthodiagraphic measurements of the heart gave: aorta 5.6 cm., right heart 7.3 cm., left heart 12.5 cm., cardio-thoracic ratio 65.4. The palpable arteries were thickened 2+, on a basis of 1+ to 4+, the arch of the aorta was uniformly widened. He had badly diseased tonsils and a chronic hyperplastic disease of both sinuses. In the hope of obtaining compensation, it was decided to remove carefully all pus foci. June 1, tonsillectomy was performed and the patient had a stormy convalescence. The degree of his heart failure increased temporarily. On June 29, a double radical antrum operation was performed without much disturbance. Following the removal of the infected tissues, compensation returned promptly and quite satisfactorily. For a year and a half he was in sufficiently good health to return to his business. He then died suddenly from acute coronary occlusion. (Photomicrographs accompany the paper "Chronic Sinus Infection in Relation to Systemic Disease," *Ann. Int. Med.*, 1931, 15, 752, Figures 12, 13, 14, 15, 16, 17.)

Case 2 (6/8/29) G. C., a man, aged 62, had suffered shortness of breath for six years, had been easily exhausted for the past four years, and worse the past month. He had had a chronic cough, nonproductive most of the time, and periodically a postnasal discharge. His blood pressure had been somewhat elevated for at least two years. Shortness of breath was the most distressing symptom. One flight of stairs had to be taken very slowly, and this exertion was accompanied by dyspnea and heart palpitation. For the past three years he had been considered primarily a cardiac case and his life had been modified to meet this condition. Undoubted cardiac pathology existed. Electrocardiograms indicated a right bundle branch block. The palpable arteries were thickened 2+, on a basis of 1+ to 4+. The arch was

uniformly widened, but the right heart measured 3 cm and the left heart 9.8 cm, and the cardio-thoracic ratio was within 50 per cent. The absence of substernal dullness pointed to the absence of definite congestive failure. Because of the absence of such failure, the possibility of chronic sepsis being the primary cause of his illness was considered. As he suffered from a pansinusitis, a double radical antrum operation, and a trans-antral ethmoidectomy on both sides were performed. There was definite hyperplasia of all the lining membranes without free pus. Symptomatic recovery was prompt. Four months after operation he reported feeling well. He had no dyspnea, and no other subjective symptoms of heart trouble. His blood pressure was 144 systolic and 76 diastolic. Three months later he again made the same report. At the present time (1934) he is still well. He is a lawyer by profession and works daily. (This case is not included in table 1 because the sinus tissues were not stained for bacteria.)

Case 3 (5/30/32) G. D. R., a business man, aged 56, was awakened at night on April 30, 1932 with acute dyspnea, which was relieved by sitting up. He experienced no pain but there was a definite sense of anxiety which left as soon as his breathing became quiet. There was no coughing or wheezing, no frothy or bloody expectoration. Shortness of breath had continued until the present time. All palpable arteries were thickened 3+, on a basis of 1+ to 4+. The arch of the aorta was sclerotic, measured 5.2 cm and was uniformly widened. The right heart measured 5.3 cm, the left heart, 8.5 cm, and the cardio-thoracic ratio was 47. The blood pressure was 92 systolic and 74 diastolic. Negative T-waves were noted in both Leads I and II. Occasional left ventricular premature beats were present. A hyperplastic sinusitis existed in both antra with a large filling defect in the right. Radical exenteration of both antra, together with a transantral ethmoidectomy, was done June 9, 1932. Complete relief from the cardiac symptoms has thus far been obtained.

Case 4 (11/22/32) G. T. K., a farmer, aged 59, had had congestive heart failure for five months, becoming progressively worse. The heart measured aorta 6.1 cm, right heart 6 cm, left heart 10.8 cm, with a cardio-thoracic ratio of 53.6. The arch was uniformly widened, sclerotic, and contained calcareous plaques. The blood pressure was 170 systolic and 90 diastolic. The palpable arteries were thickened 2+ and 3+, on a basis of 1+ to 4+. There were negative T-waves noted in Lead I, slight splintering of the S, particularly in Lead II, and T's of high amplitude in both Leads I and III. Chronic hyperplastic antrum infection existed with cyst formation in the right. It was found impossible to recompensate his heart, and, in view of this fact, radical exenteration of the sinus infection was performed. Following the operation, recompensation was obtained. During a short period of time auricular fibrillation set in, but this was broken back to a sinus rhythm with 6 grains of quinidine sulphate. During convalescence a left cerebral thrombosis of minor grade appeared, which affected the speech and the right side of the body for several days, after which time the symptoms disappeared. The patient got up and about and returned to his home. His heart again went into failure in the late summer of 1933 and he died from this cause.

Case 5 (2/1/33) G. F., a farmer, aged 66, entered the hospital with congestive failure on the basis of cardiovascular sclerosis with auricular fibrillation. He had been short of breath for three or four years. One year ago he stopped all work and has been in bed much of the time. He had severe dental sepsis and hyperplastic double antrum disease. The arch of the aorta was uniformly dilated. It measured 5.7 cm, the right heart 5.7 cm, the left heart 15.3 cm, and the cardio-thoracic ratio was over 64. The palpable arteries were thickened 3+, on a basis of 1+ to 4+. The blood pressure was 170 systolic and 120 diastolic. All teeth were removed. On March 1 radical exenteration of both antra was performed, a very pronounced

TABLE I

Sinus Tissues Examined for the Presence of Microorganisms in the Walls of Blood Vessels

| Symptoms Due to Cardiovascular Disease | | | | | | |
|--|-----|-----|---|---|---------------------------------------|--|
| Num ber | Sex | Age | Diagnosis in addition to sinus disease | Sclerosis of vessels in sinus tissues 1+ to 4+ | Diplo- cocci in vessel walls | End results |
| 1 | M | 59 | Atheroscler 4+ failure | 4+ | Positive | Improved Died 2 years later of coronary throm- bosis |
| 3 | M | 56 | Atheroscler 3+ | 4+ | ' | Good |
| 4 | M | 59 | Atheroscler 4+ failure | 4+ | ' | Improved Died one year later of congestive heart failure |
| 5 | M | 66 | Atheroscler 4+ failure | 4+ | " | Improved One recur- rence of failure and re- compensated |
| 7 | M | 63 | Atheroscler 4+ failure Toxic nodular goiter previously removed | 4+ | " | Improved Died 2 years later of congestive heart failure |
| 6 | M | 56 | Atheroscler 3+ angina | — | — | Coronary arteries 4+ Diplococci + in walls Died 2 years later of coronary thrombosis |
| Symptoms Not Due to Cardiovascular Disease | | | | | | |
| 7 | M | 60 | Atheroscler 1+ | 2+ | " | Good |
| 8 | M | 41 | Rheum endocard | Patchy 2+ | " | Improved |
| 9 | F | 40 | Atheroscler 1+ Asthma Nodular goiter | 2+ | ' | Good |
| 10 | F | 39 | Atheroscler 2+ Rheum endocard | 3+ | ' | Improved |
| 11 | M | 61 | Atheroscler 1+ Alcoholism | 2+ | | Not improved |
| 12 | M | 69 | Atheroscler 2+ Cholecystitis Prostatism | 2+ | ' | Died later Ca stomach |
| 13 | F | 60 | Atheroscler 2+ Cholecystitis Atheroscler 2+ | 3+ | | Improved |
| Microorganisms Not Found in Vessel Walls | | | | | | |
| 14 | I | 65 | Spinal arthritis Thyroid heart Mild failure Aur fibrillation Atheroscler 2+ | 2+ | Negative | Good |
| 15 | M | 49 | Arthritis Arteries 1+ | 1+ to 3+ Patchy | | Good |
| 16 | M | 64 | Neuritis Aorta 2+ | 1+ | | Died later of myeloid leukemia |
| 17 | M | 55 | Asthma Atheroscler 2+ | 1+ | | Died during attack of asthma Autopsy showed cardiovascular sclerosis of moderate grade |
| 18 | F | 64 | Arthritis Aorta 2+ Radials 1+ | 2+ | | Good |

pyogenic membrane being found particularly on the left side. The heart became recompensated and the patient returned home to remain fairly well through the summer. In October he returned once more in mild failure, and was recompensated (Figures 1 and 2).

Case 6 (3/17/30) J. W. C., a business man, aged 56, had suffered for some years with symptoms of pressure about his heart, associated with the belching of gas and

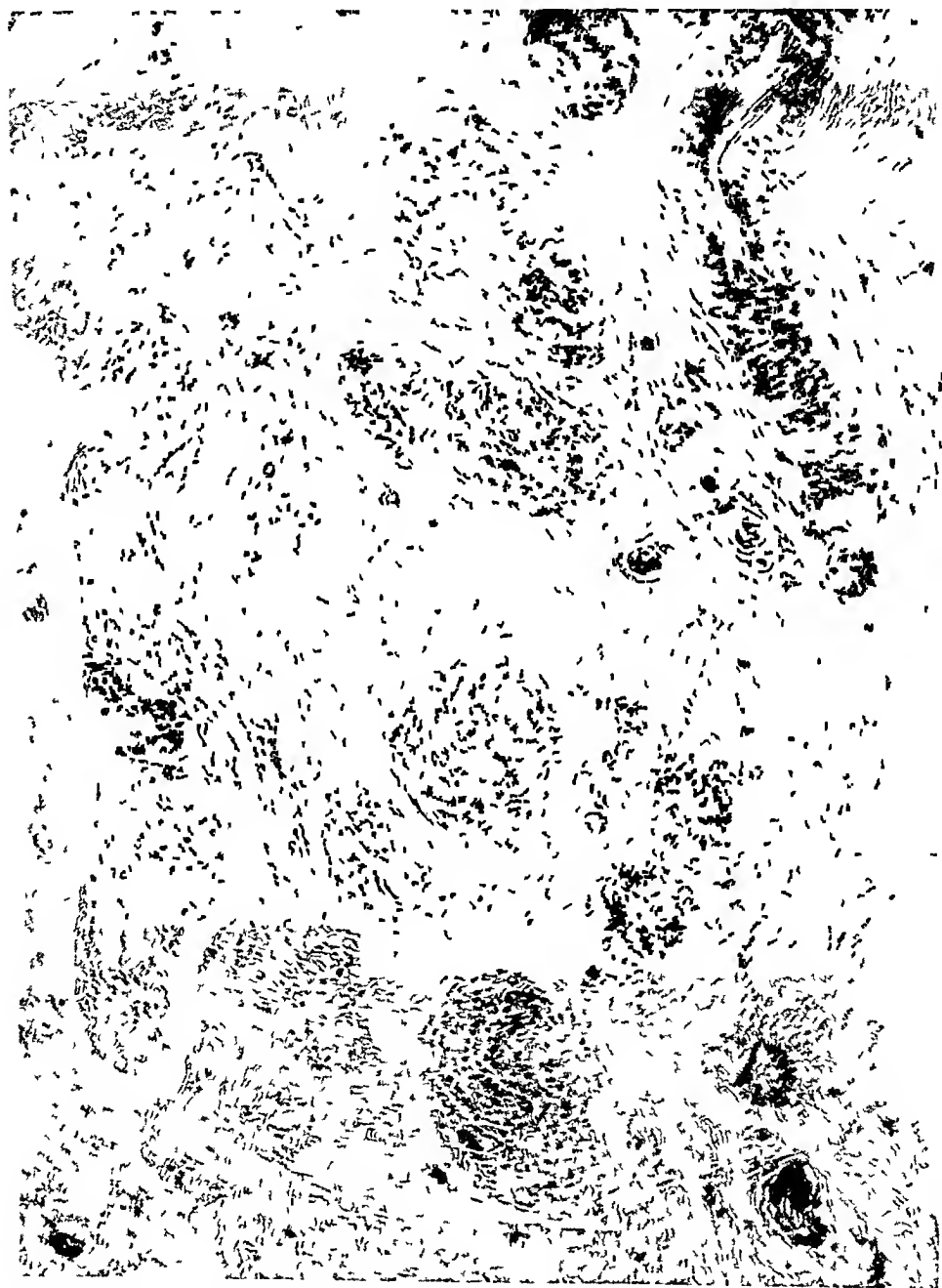


Fig. 1 (*Case 5*) Sinus membrane. Fibrosis of the walls of the small arterioles. $\times 180$

some constipation. He had suffered no symptoms of cardiac failure. His heart measurements were: aorta 5 cm, right heart 4.2 cm, left heart 10.6 cm, with a cardiothoracic ratio of 46.6. The arch was moderately widened and the palpable arteries were thickened 2+, on a basis of 1+ to 4+. Blood pressure was 186 systolic and 122 diastolic. He had a well marked hyperplastic inflammation of both antia. Radi-



FIG 2 (Case 5) Sinus membrane. Diplococci in the walls of a small arteriole, the seat of fibrosis. $\times 1900$

cal exenteration was advised but not accepted. In April 1932, he died suddenly from an acute coronary occlusion (Figures 3 and 4)

Tissues from the sinuses not only from these cases of frank heart disease but also from a number of patients suffering from other ailments have been studied with reference to the structural changes in the blood vessels of



FIG 3 (Case 6) Section of branch of coronary artery. Fibrosis and narrowing of the lumen $\times 30$

the membranes and the presence of microorganisms within their vessel walls. Data from all of the cases are given in table 1. These data reveal a rough parallelism, in the limited number of cases examined, between the finding of bacteria in the tissues and the degree of sclerotic changes present.

Microscopic Structure of Arterioles in Diseased Sinus Membranes A

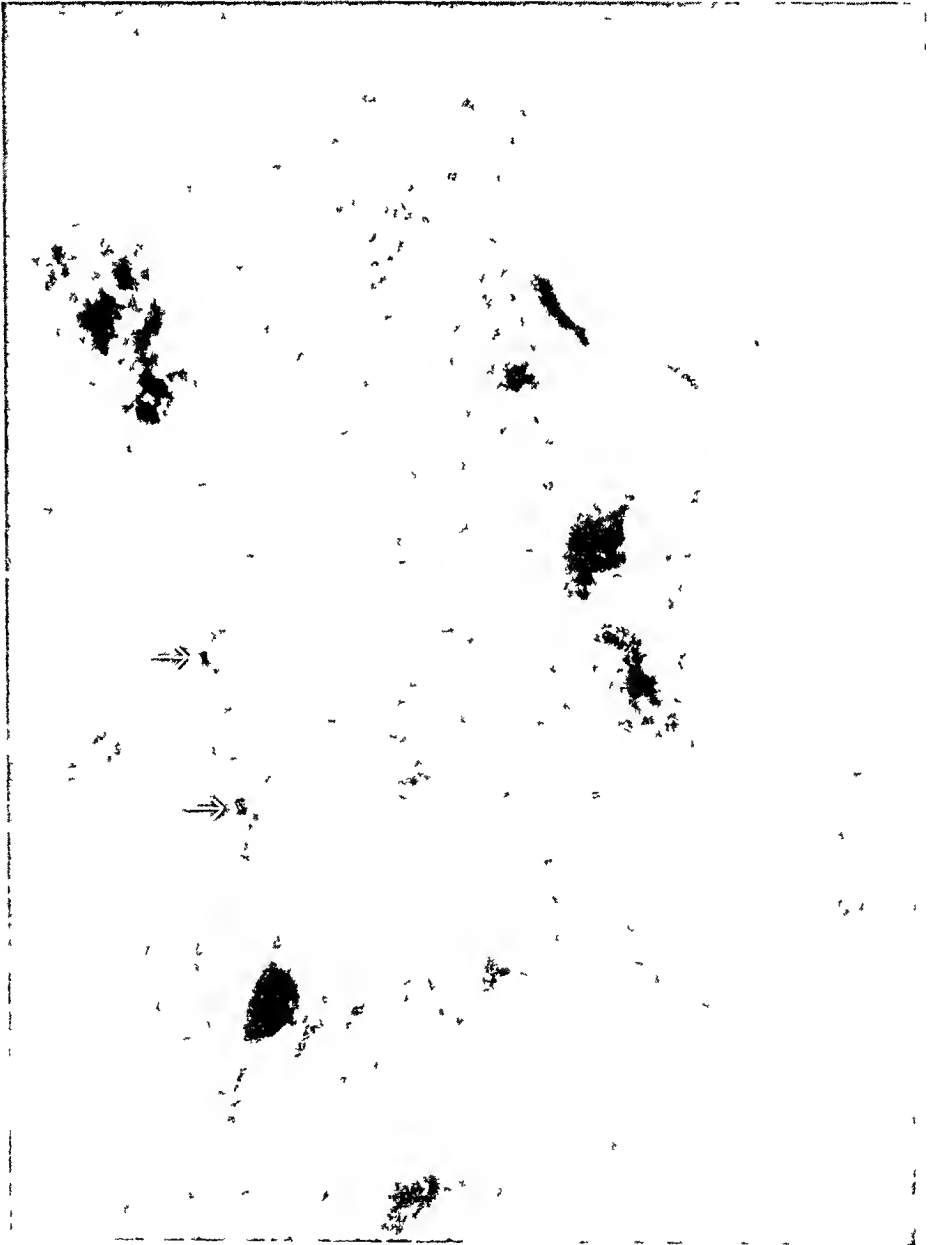


FIG 4 (Case 6) Diplococci in the wall of coronary vessel $\times 1900$

study of the histological changes in the structure of the blood vessels in sinus membranes, the seat of chronic infection, and a search for microorganisms in the walls of the vessels have been made in 18 cases*. The structural changes noted have been quite similar in all the vessels, but vary in degree. Hyaline degeneration and swelling, especially subintimal, narrows the lumen and oftentimes completely closes it. There is a diffuse proliferative fibrous tissue widening of the adventitia and media and at times the entire wall of the smaller vessels is involved in this manner. Here and there a diffuse inflammatory process with coarse fibrin deposits is noted. At times apparent edema of the media exists. There are frequently seen many polymorphonuclear leukocytes in the zone between the intima and the media. Small round cells and plasma cells occur in some areas but histiocytes are as a rule few in number. In Case 7 there are, however, numerous histiocytes, small round cells and a few eosinophiles around and in the walls of many of the vessels.

Bacterial stains reveal numerous microorganisms in the sinus membranes. Many of these organisms are found in the walls of the small arterioles, both in the subintimal proliferations of fibrous connective tissue and in the outer media and adventitia. These organisms are all in the form of small diplococci which have the morphology and staining reactions of streptococci. They are frequently found close to the collections of small lymphocytes and plasma cells in the tissues of the blood vessel walls.

The microscopic structure is that of a diffuse subacute arteritis.

Microscopic Structure of Coronary Arteries in Case 6 (Figures 3 and 4) Tissue blocks, taken from the heart shortly after the death of this patient, were kindly sent to us by Dr. G. F. Strong of Vancouver, B. C. Gross

* Tissue stains used were

1 Giemsa stain—standard technic

2 Maximow's hematoxylin, azure eosin

3 Azin carmine

4 Hematoxylin and eosin

Technic of Staining for Gram Positive Bacteria in Tissues All tissues were immediately fixed in Formo-Zenker's solution upon removal in the surgery, and were later embedded in paraffin. Sections were cut 5 micra thick. They were treated with xylol, alcohol, water, Lugol's solution, sodium thiosulphate and water. After the water, the sections were stained for 2 minutes with ammonium oxalate crystal violet, washed in water, destained in 80 per cent alcohol until a very pale blue, run through alcohol, xylol and mounted in balsam.

Bacteria show a deep purple color against an almost colorless tissue background.

Crystal violet formula

Crystal violet 20 gm

Alcohol 95% 200 cc

Amm oxalate 1% 900 cc

Dissolve and filter

Formo-Zenker solution

Formalin 40% 5 cc

Zenker's sol 95 cc

Lugol's solution I KI H₂O 1 2 100

The proper staining of bacteria in tissues is attended with much difficulty. This is the reason for detailing the technic used. Dr. E. C. Rosenow, Mayo Foundation, first taught us a satisfactory method after over a year had been spent with indifferent results. Later A. L. R. perfected the above technic which gives uniformly well stained preparations.

We would also here acknowledge our indebtedness to Dr. Frank R. Menne, Head of the Department of Pathology, for his assistance and criticism.

examination of the heart revealed the following "The heart was examined without removing it from the body It is but slightly enlarged The aorta is of normal width and appearance throughout The valves are all intact, although there is considerable sclerotic thickening in the aortic cusp of the mitral valve The coronary arteries are markedly narrowed

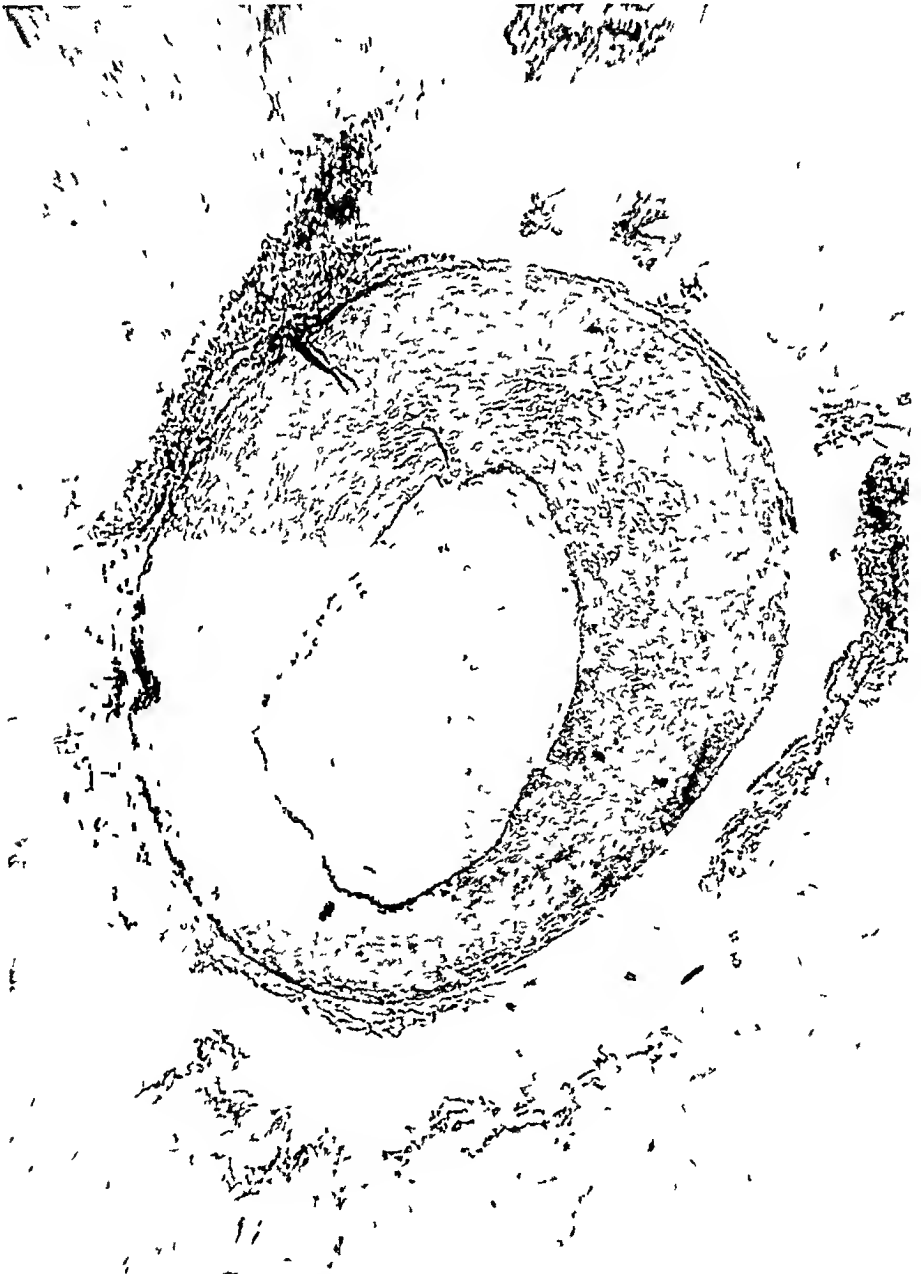


FIG 5 (Case 9) Coronary artery from case recorded in table 2 $\times 300$

and sclerotic. Approximately 1 inch from the orifices of both right and left coronaries, the vessels appear almost completely occluded, admitting barely the point of a pin. About 1 inch from the orifice of the circumflex branch of the left coronary there is a fresh organized thrombus, which completely occludes the lumen. It is about 1 cm. in length, quite firmly ad-



FIG 6 (Case 9) Coronary artery Diplococci in fibrosed vessel wall $\times 1800$

herent to the walls and to the site of an atheromatous plaque The heart muscle is of fairly good consistency ”

The lumen of the artery shown in figure 3 is markedly narrowed and slit-like This is caused by a thickening of the wall due to a subintimal proliferation of fibrous connective tissue In this area there are numerous



FIG 7 No S-96-34 Small arteriole within muscular layer of gall-bladder from a case of subacute cholecystitis Arteriole shows fibrosis of its wall $\times 300$

collections of small lymphocytes and plasma cells as well as cholesterol crystals. There is some edema in the areas where the chronic inflammatory cells are in greatest numbers. The outer media and inner adventitia are also involved by a fibrous connective tissue proliferation. Here there are likewise collections of small lymphocytes around the outer adventitia. Here are also a few dense collections of chronic inflammatory cells. Some of the small arterioles in the adventitia have markedly narrowed lumens due to the same proliferative process. Numerous diplococci are visible in specially stained sections. They are found to be most numerous around and in the dense collections of lymphocytes. These microorganisms have the same morphological and staining characteristics as those found in the sinus tissues and those seen in tissues taken from patients dying of streptococcic septicaemia.

The microscopic structure is that of subacute arteritis with atheromatous degeneration.

Microscopic Structure of Coronary Arteries from Autopsy Material Taken from Patients Dying from Acute Coronary Thrombosis (Figures 5 and 6) For comparison with the microscopic picture seen in the coronary arteries in Case 6, we examined the material obtained at postmortem from 11 unselected patients dying from acute coronary thrombosis (Table 2).

In all sections there is some degree of atheromatous degeneration, but in no instance is this process advanced enough to cause marked narrowing of the vessel lumens. The lumens of the vessels are filled by fresh thrombi in all cases except one (3). In this case organization with recanalization has taken place. The fresh thrombi are adherent to the endothelial lining of the vessels and are formed by intact blood cells in a matrix of fibrin and platelets. The intima is greatly thickened due to proliferation of fibrous connective tissue. The media and adventitia are thin. In this subintimal proliferation and also in the outer media and adventitia there are varying numbers of small lymphocytes and plasma cells. In some places these chronic inflammatory cells are clustered close together and in other places are widely scattered. In a few instances, where larger arterioles were found, there is seen a marked subintimal proliferation causing narrowing of the lumen, and, in the adventitial area, collections of small lymphocytes. Bacterial stains of these tissues reveal varying numbers of diplococci and in a few instances single and short chain cocci. These organisms are found in the subintimal proliferative areas and in the outer media and adventitia. In some sections they are visible in the adventitia of the walls of the arterioles. The organisms are found for the most part in close relation to the denser collections of small lymphocytes.

The microscopic structure, again as in Case 6, is that of subacute arteritis, with atheromatous degeneration.

In the 11 cases chronic cholecystitis was present three times and a severe grade of pericemental infection and chronic sinus disease each twice.

TABLE II
Coronary Arteries from Acute Cases of Coronary Occlusion Showing the Incidence of Bacteria in the Vessel Wall

| Case Number | Age | Sex | Branch of Coronary Artery | Sclerosis of Basis 1+ to 4+ | Histology of Intima | Histology of Media | Histology of Adventitia | Character of Thrombus | Thickness of Vessel Wall | Edema of Wall | Infiltration | | Microorganisms | | | Other Pathology Found at Autopsy |
|-------------|-----|-----|---------------------------|-----------------------------|--|--------------------|-------------------------|-----------------------|--------------------------|---------------|--------------|----------------------------|----------------|-------------|------------------------------|---|
| | | | | | | | | | | | Amount | Type | In Wall | In Thrombus | Type | |
| 1 | 70 | M | Left | 2+ (hyaline) | Infiltrated very thick fibrous hyaline | Thick fibrous | Thick hyaline | Fresh formed | 0.5-1.0 mm | 0 | 3+ | S lymphocytes plasma cells | 2+ | 0 | Diplococci | Cholecystitis with cholelithiasis |
| 2 | 65 | M | Left | 2+ (calcified) | Infiltrated thick fibrous atheromatous deg | Thin | Thin | Fresh formed | 1.0 mm | 0 | 2+ | S lymphocytes | 2+ | 0 | Diplococci | Chronic cholecystitis Chronic fibrous appendicitis Arteriosclerotic kidneys |
| 3 | 70 | F | Left | 2+ | Infiltrated slight atherom degeneration | Thin decelerated | Thin | Recanalized thrombus | 2.0 mm | 2+ | 1+ | S lymphocytes | 2+ | 2+ | Diplococci | Chronic cholecystitis Chronic pleuritis |
| 4 | 50 | M | Right | 2+ | Infiltrated thick atheromatous deg | Thin infiltrated | Thin | Fresh | 2-3.0 mm | 1+ | 3+ | S lymphocytes | 2+ | 0 | Diplococci | Pyorrhea and chronic antral infection Purulent bronchitis |
| 5 | 60 | M | Left | 2+ (calcified) | Thick infiltrated atheromatous deg | Thin | Thin | Fresh | 0.5-2.0 mm | 1+ | 2+ | S lymphocytes plasma cells | 3+ | 2+ | Diplococci Short chain cocci | Many carious teeth |
| 6 | 43 | M | Right | 2+ (calcified) | Thick hyaline-fibrous atheromatous deg | Thin | Thin | Fresh | 2.0 mm | 0 | 1+ | S lymphocytes | 2+ | 0 | Single and diplococci | Chronic pleuritis Mucopurulent bronchitis Clinically nasal congestion Asthma—septum resection |
| 7 | 60 | F | Left | 3+ (calcified) | Thick hyaline not infiltrated atheromatous deg | Very thin | Very thin | Fresh | 0.5-1.0 mm | 0 | 0 | 0 | 1+ | 0 | Diplococci | Arteriosclerotic kidney Chronic hyperplastic endometritis |
| 8 | 87 | M | Left | 2+ (calcified) | Infiltrated thick calcified atheromatous deg | Thin | Thin | Fresh | 2-3 mm | 1+ | 1+ | S lymphocytes | 1+ | 0 | Single and diplococci | Sero fibrous pleuritis with effusion Semicarditis sclerosis |
| 9 | 50 | M | Left | 2+ | Infiltrated thick hyaline fibrous | Thin | Thin | Fresh | 1.0 mm | 0 | 2+ | S lymphocytes | 1+ | 0 | Diplococci | Healed duodenal ulcer |
| 10 | 60 | M | Right | 2+ | Infiltrated very thick atheromatous deg | Thin | Thin fibrous | Fresh | 2.0 mm | 0 | 1+ | S lymphocytes | 2+ | 0 | Diplococci | Fibrous pleuritis Fibrous pericarditis |
| 11 | 70 | M | Left | 1+ | Infiltrated atheromatous deg | Infiltrated thin | Infiltrated thin | Fresh | 2-3.0 mm | 0 | 3+ | S lymphocytes | 2+ | 0 | Diplococci | Fibrous pleuritis Arteriosclerotic kidneys |

Microscopic Structure of Arterioles in the Wall of the Gall-Bladder, the Seat of Subacute Cholecystitis (Figures 7 and 8) Because of the apparent clinical relationship occasionally seen between diseases of the gall-bladder and frank heart disease we studied the arterioles found in the smooth muscle layer of the gall-bladder in 12 cases of subacute cholecystitis. All of the



FIG 8 No S-96-34.

of subacute

gall-bladders were removed at operation and placed immediately in Formo-Zenker's fluid. The clinical history of the following case is illustrative of the type of heart disease we have in mind.

A housewife (11047) 49 years of age, entered the hospital in February 1926 in severe congestive failure on the basis of a chronic hypertensive cardiovascular sclerosis with auricular fibrillation. She had first become breathless two years before, since which time she had not been well, and definite congestive failure had existed since August 1925. During most of this time she had been in bed. She had had attacks of gall-stone colic in 1915 and 1920. Following the first attack of colic the gall-bladder had been removed. Recompensation of the heart under control was not obtained, and during this period of treatment the patient suffered an attack of right upper quadrant abdominal pain with fever and slight jaundice, indicating the presence of common duct obstruction. She was operated upon in the presence of the heart failure and a common duct drainage instituted. Following the operation the heart became quickly recompensated and at the present time (1934) the patient is still living. In 1927 she went through a severe bronchopneumonia without again decompensating the heart. For a time the fibrillation was removed by quinidine sulphate but for the past two years it has been refractory to such treatment. At the time of first measuring the size of the heart, the orthodiagraphic measurements were: aorta 6.3 cm, right heart 5.9 cm, left heart 10.7 cm, cardio-thoracic ratio 57.0. One year later the measurements were: aorta 6.3 cm, right heart 5.7 cm, left heart 8.4 cm.

The small arterioles of the gall-bladders examined (figures 7 and 8) all present a subintimal fibrous connective tissue proliferative process which has caused a marked narrowing of the vessel lumen. Numerous small lymphocytes are found in the subintimal area. The outer media and adventitia are increased in width due to a fibrous connective tissue proliferation. Numerous diplococci are found in these proliferative areas. These microorganisms have the same morphological and staining characteristics as those found in the sinus membranes and coronary arteries. The microscopic structure, again, is that of a subacute arteritis, often obliterative.

In order to compare the blood vessel changes in the presence of chronic pus infection in other more distant tissues, examination of sections from a papilloma taken from the urinary bladder, the seat of a chronic inflammatory process, and sections from chronic cutaneous ulcers, caused by pyogenic microorganisms, were made. All of the small arterioles in the sections studied have thickened walls which have caused a marked narrowing of the lumens. The widening of the wall is due to a subintimal fibrous connective tissue proliferation. The media and inner portion of the adventitia are likewise involved by the same process. There are numerous small lymphocytes and a few plasma cells scattered throughout the vessel walls and diplococci are likewise present. The process is a subacute arteritis.

COMMENT

It is unnecessary to review in further detail the structural changes found in the blood vessels of the sinus membranes, the hearts, the gall-bladders, and the two other tissues presented in the text. These changes are seemingly

comparable to those described in experimental animals by a number of investigators. Especially interesting are the experimental lesions of the aorta and other arteries produced in rabbits by Benson, Smith and Semenov³ by the repeated intravenous injection of streptococci over a long period of time. A comparison of their photomicrographs of the more chronic lesions with our own shows a striking similarity. We have not attempted to read into our findings the role of chronic infection as the primary factor in the causation of arteriosclerosis. We have discussed a small group of patients with congestive heart failure on the basis of chronic cardiovascular sclerosis in whom recompensation could not be obtained until after the removal of a coexisting chronic sinus disease. The character of the arterial lesions is described and the fact is stressed that diplococci having the morphological and staining characteristics of streptococci are present in considerable numbers in the arterial walls. The method of removal and fixation of the sinus membranes removes the criticism of possible postmortem invasion of these microorganisms. We have, moreover, considered these microorganisms to be streptococci because we, and our associates,⁸ have cultured more than 400 sinus membranes from cases of chronic paranasal sinus disease and have found the predominating microorganisms to be streptococci. They were present in 94.5 per cent of the sinus membranes cultured, 35 per cent were identified as *beta*-hemolytic streptococci, 33 per cent as *alpha*-hemolytic green producing streptococci, 14 per cent as *Streptococcus viridans*, and 18 per cent as non-hemolytic streptococci of the *gamma* type. Other microorganisms occurred in combination with the streptococci but with minor frequency. One cannot, likewise, very well consider the mechanical factor of stress and strain to be of importance in the small arterioles of such tissues. Chronic hypertension was not present in all of the patients. One, Case 3, had a persistently low blood pressure, 92 millimeters of mercury systolic and 74 diastolic. As regards the influence of cholesterol we found cholesterol deposition in the walls of many vessels but it seemed to be less prominent than the inflammatory changes present. It is generally assumed now that heavy cholesterol feeding over a sufficiently long period of time will produce arteriosclerosis in rabbits. The work of a number of investigators would tend to show this. Benson and his co-workers were unable to produce arteriosclerosis in their rabbits by cholesterol feeding alone but when such feedings were given together with repeated induced infections, the changes in the arteries were much more marked than those due to infection alone. The thought behind our work has been that if chronic pus infections can be reasonably shown to have some relationship to the cause of this form of so-called degenerative heart disease, then the early prophylactic removal of such infections may lessen the number of coronary heart deaths now seen so frequently in the middle decades of life.

SUMMARY

We have presented a small group of patients showing congestive heart failure on the basis of a chronic cardiovascular sclerosis, in whom recompensation could not be obtained until after the removal of a coexisting chronic sinus disease. We have described lesions in the arterioles of the sinus membranes removed by operation in these patients and have referred to them as being comparable with the arterial changes found in the heart and some other organs in both human and experimental animal material. The fact that microorganisms having the morphological and staining characteristics of streptococci were constantly found in comparatively large numbers within the walls of the arteries in all the tissues studied has been emphasized as suggesting a possible etiologic relationship.

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AN EXPLANATION OF THE MECHANISM OF INFANTILE PARALYSIS PRODUCTION IN THE HUMAN BEING¹

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PART I

FABER¹ believed that a good theory for the explanation of the virus spread in poliomyelitis in man would be to assume that, after the virus entered the system along the olfactory terminal fibers, it spread by way of the olfactory tracts, through the hypothalamus, to the medulla, thalamus and midbrain, and then down the spinothalamic tract to the posterior column, finally reaching the anterior horn cell area in the cord. However, the possibility of extension by other pathways was not denied. His hypothesis was based upon clinical findings and upon evidence that was obtained from experiments on monkeys that had contracted the disease following intranasal instillation of poliomyelitis virus.

In the majority of human beings and monkeys, paralysis first develops in the muscles that receive their nerve supply from the lumbar enlargement and only secondarily in those whose nerve supply comes from the cervical area. This fact forms the basis for a fundamental objection to Faber's theory of virus spread, since it would be difficult to understand why the virus would travel down the spinothalamic tract in the cord, skip the cervical enlargement, and in most instances involve first the lumbar enlargement and paralyze first the muscles of the legs.

The spinothalamic tract carries pain and temperature sensations in the lateral column and touch and pressure in the ventral branch. The ventral fibers are not involved in this disease, since touch and pressure seem to be normal. As both fiber tracts run together in the spinal lemniscus, an almost anatomical predilection for the lateral tract would have to be presupposed to explain the absence of involvement of the ventral fibers, unless some other logical reason presented itself.

It is claimed that the hyperesthesia that appears sometimes before somatic paralysis suggests a prior localization of the disease in the spinothalamic tract. When I analyzed our cases I found that 63, or 14 per cent had hyperesthesia or pain, in 58 of these cases, the hyperesthesia occurred in response to deep pressure only and was usually limited to those muscles and tendons of muscles that later became paralyzed. The hyperesthesia was in the muscles and about the tendon ends and not in the skin. Stimulating the skin by stroking it lightly would only occasionally elicit pain (five cases). In other words, although the muscle tendons were painfully

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hyperesthetic on manipulation, the skin areas that had their nerve supply from the same segments were not hyperesthetic. This dissociation of light from deep sensibility may be the result of conditions other than the involvement of the spinothalamic tract per se.

Pain was occasionally present when pressure was applied over the vertebrae or when they were gently pounded, this was usually the case in the absence of any skin hyperesthesia.

The appreciation of temperature has always been normal in our clinical experience, although the skin of the leg or arm that is paralyzed may be colder than that of the non-paralyzed member. This, however, is an objective finding and may be totally unassociated with any central sensory lesion of the cord and may be easily explained on the basis of vasomotor phenomena secondary to a nerve irritation such as is seen in other types of paralyses. Though the skins of our patients were colder than is normally the case, all of those who were able to cooperate could easily tell the difference between heat and cold, an unlikely finding if the lateral spinothalamic tract were consistently involved. I do not think that Muller's observations on temperature dissociation would be agreed to by other clinicians.

The fact that no plausible reason is given as to why the disease is localized in the lumbar area and the fact that there is no good explanation as to why the mesenteric glands are sometimes enlarged cast some doubt also on Faber's theory of virus spread in the human, although one cannot deny that it may thus spread after the virus has been intranasally instilled.

Ataxia is mentioned in Faber's monograph. None of our patients ever had acro- or proximo-ataxia, since they always appreciated their position in space. Only occasionally, some of our patients seemingly had asynergy of movements somewhat athetoid in type, and even fibrillary twitchings have been seen, these might well have been clonic or tonic spasms, the causation of which might have been something totally remote from a lesion of the lateral spinothalamic tract. The most important point, however, is that these twitchings, though the rule in experimental monkey paralysis, were the exception in humans. The other points enumerated by Faber could all be explained on anatomical bases, totally different from those he presented in his classical monograph.

Flexner² has stated that the "small olfactory filaments" of the nasal area "are advantageously placed to act as the means of transportation of the virus." Faber¹ referred to the importance of the unbroken connection of the olfactory nerve, and it is here that Flexner and Lewis³ and others have experimentally shown that absorption may take place, since they reproduced the disease by packing the nasal passages with gauze that had been soaked in poliomyelitis virus.

The olfactory nerves, consisting of unmyelinated grey fibers, with their 20 to 30 olfactory filaments, are not the only unmedullated fibers in the region of the cribriform plate, for it is precisely here that the *nervus terminalis* is "peripherally hypertrophied in man as compared to the known de-

velopment in other mammals" ⁴ The olfactory area contains approximately 1500 cells of the terminal portions of this nerve situated under the nasal mucosa, cells which with their processes make a vast interlacing network of unmyelinated tissue and whose fibers *end in the ganglion terminale on the olfactory bulb* Significant indeed is the assertion made by Brookover that the "grouping of cells and fibers" is "such as might be found in the myenteric or submucous intestinal sympathetic" ⁴ Most significant for us, is the similarity of the peripheral nervus terminalis to an enteric plexus ⁵

The olfactory area is peculiar in that it contains a mass of unmyelinated nerve tissue of the type which usually absorbs the poliomyelitis virus The thirteenth cranial nerve and the olfactory fibers lie near or at the embryological upper end of the foregut at the juncture of the stomodeum Fibers similar to the thirteenth nerve are found in the hindgut and, if morphological similarity is significant, the latter fibers should also attract the virus The only apparent reason why the gastrointestinal tract is not seriously considered as a portal of entry for the virus is that experiments on virus transmission by way of the gastrointestinal tract have hitherto been contradictory

PART II

Where would the portal of entry of this disease be located in the human? It is conceived that it could be any place where the virus could easily and normally come in contact with either the grey nerve fibers or the axis cylinders of myelinated nerves The disease is produced when the injection of the virus is made directly into the sciatic trunk after irritating the nerve with the injecting needle so that the axones are exposed to the virus ^{6 7 8}, when intracerebral injections are employed, when the virus is injected intraperitoneally ⁹, when the virus is injected intraocularly ¹⁰, when intraspinal ¹¹ and intracisternal injections are made ¹² and when intranasal instillation is employed—all injections having been made in locations where unmyelinated fibers abound When the gastrointestinal route has been used as a portal of entry, some isolated successes ¹³ and, on the other hand, many failures ¹⁴ have been reported When one studies the role that the skin plays as a portal of entry, one finds that virus inoculations are relatively innocuous, ¹⁰ that it is difficult to produce the disease by subcutaneous inoculations, ¹⁵ but that infection may be consistently brought about by intracutaneous injections of the virus ¹⁶ The unmyelinated end fibers are not present in the epidermis nor to any great extent in the subcutaneous area, but they do ramify in the corium, which would be the logical place from which absorption should take place if the virus were absorbed from any spot where the naked grey fibers predominate One could almost postulate that the virus has nearly an obligate affinity for grey nerve fibers

An area from which absorption could take place may be present where there are grey fibers, but a "take" would depend upon an unbroken connection between the absorbing area and the central nervous system, that is, either

on the possibility that the virus could be transferred from the area of absorption to the central nervous system along an axis cylinder pathway⁶ or that it could reach the central nervous system before it would be absorbed and excreted by the host. One might surmise that the rate of absorption of the virus, the ease of its transmission, its virulence, etc., would also be factors tending either to impede or to accelerate the production of the disease. The most direct routes to the brain and cord for the experimental production of the disease are by way of the olfactory and terminalis nerves, and after intrasciatic and intracerebral injections of the virus. Where the connection is definite and the course immediate, the disease is produced easily in the experimental animal. The observation could be made that, aside from a peripheral absorbing area of grey fibers or axis cylinders of medullated nerves, a convenient connection with the central nervous system must be present in the experimental animal and in the human. In this light, there are only three places in the body that could qualify as natural portals of entry, i.e., either by way of the nasal mucosa, the gastrointestinal tract, or the respiratory tract (lungs). But few experiments have been done in which the lungs have been used as a portal of entry, and confirmed evidence is lacking that would show them to be areas that would absorb the virus of infantile paralysis.

Many experimenters have tried and have failed to reproduce the disease from the gastrointestinal tract. I felt that the reason for this failure lay in the fact that the virus never approximated the grey fibers, since, after its introduction through a tube or a needle, the virus emulsion was usually swept on, out of the small intestine and into the colon. Accordingly, I exposed the abdominal cavities of monkeys, clamped the small intestine in one place with a pair of intestinal clamps a few inches above the ileocecal valve and in another place about a foot or more above this. While the clamps were held in place, a potent virus suspension was introduced into the isolated portion of the intestinal canal through a 24 gauge needle until the gut was ballooned out and the intestine was kept tense until the pinch reflex had disappeared. Poliomyelitis developed.¹⁷

Even though the dose had been intestinally injected, the animals might have regurgitated some virus and thus might have infected the olfactory area. Since the postganglionic fibers of the sympathetic system are unmyelinated, at least to the abdominal plexuses, and the fibers of the intestinal blood vessels are possibly unmyelinated as far as the vertebral ganglia themselves, there was no reason why the disease could not be reproduced by a subserosal injection of the virus. Accordingly, the abdomen was opened, a potent virus suspension was injected subserosally at multiple points and the disease was produced.¹⁷ It is curious that when proper doses of poliomyelitis virus are injected subserosally, the disease that develops in monkeys is more like that seen in humans, since only a monoplegia may result, in marked contrast to the fulminating quadriplegia seen in the experimental animals after intracerebral injection or intranasal instillation of the virus.

One could surmise that the spread of the virus to the cord in such animals as developed poliomyelitis when the gastrointestinal tract was used as a portal of entry was by way of the sympathetic system

In my clinical studies, I have observed modifications of reflexes which can be best explained as being due to an involvement of the sympathetic system followed later by an irritation of the involved somatic nerve, in short, a postganglionic lesion of the sympathetic system followed by a somatic nerve lesion¹⁸ That this conclusion was not unusual was shown when I studied the same reflex responses in a comparable gastrointestinal disease, typhoid fever, and found that they were involved in the same manner in the severely ill patient¹⁹

In my clinical experiments, I found that following pilocarpine injection the sweat gland secretion was increased over those skin areas that corresponded to the paralyzed somatic segments I found, also, that when those patients who had had pilocarpine injections were injected with adrenalin, sweating ceased over the skin areas of the unaffected muscles, while it continued over the segments of paralyzed nerves, indicating clearly that the thoracolumbar sympathetic system did not function for the involved segments,²⁰ again evidence that the sympathetic system is involved

Monkeys injected intrasciatically with virus contracted the disease Control monkeys whose sciatic nerves had been tied, cut and then injected with virus in the distal portion did not contract the disease The spinal cords of monkeys were transected in the region of the tenth thoracic segment, the sciatic nerve was then injected with poliomyelitis virus and the animals contracted the disease The spread of the virus in this case to the arms, etc., was by way of the sympathetic system, the only nerve connection not disturbed⁸ When the cord was cut and the virus injected intracerebrally, the virus was occasionally found in the distal lumbar portion, again an illustration of spread by way of the sympathetic system²¹

Clinically, the sympathetic system is involved before the somatic, since paradoxical urinary retention with dribbling and obstinate stasis of the gastrointestinal tract often occurs before somatic paralysis is noted²²

For anatomical reasons, it is not illogical to assume that the virus first involves the sympathetic system in the human The somatic nerves have no direct white fiber interpositions in the areas from the second lumbar to the second sacral segment and none upward from the first thoracic segment Here there are immediate grey fiber connections only and it is in these segments of the cord that involvement occurs One can hardly explain the spotty spread of a disease by a virus that travels up or down the cord and that involves first the lumbar section of the cord and then the cervical It could be explained, however, if one presaged a spread of the virus from the gastrointestinal tract by way of the sympathetic grey fibers to the sympathetic ganglionated chain, then down to the lumbar area where no white rami are present and to the somatic nerve In more marked involvements, the spread would be up along the sympathetic collateral chain to the only other place that lacks white rami communicantes, i.e., the cervical cord

We should and do find most of the paralysis in the human in those muscles whose innervation comes from the lumbar and cervical enlargements. Only when the disease is massive would it involve those segments which have connector fibers (white fibers), namely, the thoracic and abdominal. Involvement of the postganglionic vagal fibers yields little clinical information, unless it be subjective. Nevertheless, in the severely toxic case, one can picture an involvement of the preganglionic vagal fibers with the upward spread of the virus, a simulation of the clinical condition of bulbar palsy.

If in the human the virus is arrested at the nerves where white fiber interpositions occur, then much paralysis would not be seen in those muscles whose innervations are below the second sacral segment. Usually the patient should be able to move the big toes, and the levator ani, coccygeus and other perineal muscles should not be affected in the ordinary case. The fingers could likewise be flexed when the arm muscles are involved. This is exactly what is usually seen in the average clinical case.

Physiologically, the early reflex changes in this disease could be best explained as an early involvement of the sympathetic system.¹⁸ The loss of the abdominal reflex response followed by hyperactive knee jerks with or without weakness of the quadriceps muscle, in turn succeeded by loss of the knee jerk reflexes, all have their counterpart in physiological experiments. If sympathetic stimulation increases tone, how would it be affected by thoracolumbar disconnection? The muscles of sympathectomized animals are soon fatigued. Such muscles tire easily when activated, although they may be wholly under voluntary control and still have a simple somatic spinal arc intact. It is reasonable to suppose that the stability of the reflex arc and its ability to withstand fatigue, depend, to some extent at least, upon the presence of an integrated sympathetic system.

PART III

After intrasciatic, intranasal or intracerebral introduction of a virulent poliomyelitis virus in monkeys, the disease comes on within four to seven days. When I injected the virus directly into the lumbar cord itself, the animals did not become paralyzed at once, two and a half days elapsing before this condition was noted. Why should there be such a delay? The fact that the virus can be absorbed and be present in doses lethal for monkeys in the tissue of the cord, medulla and even brain long before the production of somatic paralysis in this animal is indeed peculiar. It argues for the fact that the virus, though easily absorbed by grey fibers and transmitted to the brain and cord along axonic pathways, does not immediately produce pathological changes in its passage of sufficient intensity to result in clinical evidence of disease. This is true even of the experimental animal.

Though the virus initiates the disease, there are some clinical and experimental findings which make one wonder whether the virus alone is the sole

cause of the entity known as infantile paralysis. Other diseases, such as swine influenza²³ or oroya fever,²⁴ are produced by a combination of factors. Perhaps poliomyelitis also is such an infection.

When I first became interested in poliomyelitis, I thought that the virus ought to be obtained easily from the feces of patients who had the disease. I tried to recover it from the stools but failed. If the virus has an obligate affinity for grey fibers, the probabilities are that it would be absorbed by the nerve fibers and stay fixed in the nerve tissue. Such virus as was not absorbed would be excreted by the gastrointestinal tract long before symptoms started and hence would not be found in the feces when paralysis came on. I found, however, that the stools obtained from patients ill with poliomyelitis during the acute stage of the disease were much more toxic than were those obtained from the same patients during convalescence. Apparently something was manufactured in the stool during the course of the disease that was more toxic to guinea-pigs, something that was not present in normal stools, and yet it was equally obvious that this something was not the virus of poliomyelitis.²⁵ When urine was taken from patients at the height of an attack of poliomyelitis and injected subcutaneously into guinea-pigs, the local reactions that followed such injections were more severe than those that followed injections of normal urine.

Stools collected from young monkeys were emulsified and injected subcutaneously into guinea-pigs; there were but slight local reactions. Stools collected from the same monkeys after they had contracted infantile paralysis showed a very definite increase in toxicity in that the abdominal areas of the guinea-pigs injected with this emulsion might slough and the animals might even die.²⁶

It occurred to me that a secondary factor must be present before the clinical condition of infantile paralysis could be produced. The colon bacillus was considered in this light. I studied the agglutination titer value contained in the blood serums of poliomyelitis patients, taken at the height of the disease and later during convalescence, and found that there was a marked difference, since the agglutination titer was much less for the enteric group in the serums taken at the height of the disease than it was for those taken during convalescence.²⁷ It was not possible at the time to say whether the agglutination titer values were lowered with disease and returned to normal with recovery, or whether the titer was lowered before the disease occurred and increased with recovery.

The young macacus Rhesus monkey is very susceptible to poliomyelitis and has little or no agglutinins in the blood serum against the colon bacillus. Curiously, as the animal gets older, its serum agglutinin titer for colon organisms becomes higher. It is also curious that such animals become more refractory to the same unit dose of virus as they grow older. I immunized young monkeys artificially in order to increase their titer value and then injected them with potent poliomyelitis virus. When they contracted the disease the agglutinin titer of their blood serum decreased, and im-

POSSIBLE METHOD OF VIRUS SPREAD IN INFANTILE PARALYSIS

| Phase | Position of Virus | Symptoms |
|-------|---|--|
| I | At first the virus is free in the gastrointestinal tract | There are none, or possibly some with diarrhea and pain |
| II | The virus becomes fixed in the unmyelinated postganglionic fibers of the thoracolumbar outflow | The abdominal reflexes are absent or modified. There is constipation possibly, indefinite pain in the belly. There is pain over the back too. |
| III | The virus spreads from the sympathetic system to the somatic segmental nerve | In addition to the symptoms described in Phase II, there is hyperactivity of the reflexes with tiring on repeated stimulation. |
| IV | The virus, spreading backward over the somatic segmental nerve, reaches the spinal ganglia | In addition to the symptoms described in Phases II and III, there is segmental pain in the muscles and tendons that are supplied by the nerve of the segments involved. |
| V | About this time, the virus begins to be absorbed and excreted by the urinary bladder | A peripheral type of urinary bladder paralysis may now appear with overflow dribbling when the virus factors present are absorbed by the terminal grey fibers of the bladder and its neck, whether of the sympathetic or parasympathetic system. |
| VI | The virus reaches the cord and involves the anterior horn cell | In addition to the symptoms described in Phase V, the reflex reactions now become diminished or lost. Muscle paresis or paralysis appears. |
| VII | The virus travels up the sympathetic chain to involve the cervical area | Here the train of events is the same as outlined in Phases III and VI. |
| VIII | The virus may be virulent enough to be absorbed directly by the vagus nerve | A condition simulating bulbar palsy appears. There is dysphagia, dysarthria, etc. |
| IX | The virus may travel along the grey fibers of the sympathetic system, or by a cord pathway to the medullary, the internal capsular and the cortical areas | The symptoms here would depend upon the localization of the virus, with bulbar palsy, hemiplegic and encephalitic reactions, respectively. |

mediately before their death the agglutinin titer value was practically nil. From the results found in the human and from those obtained in experiments with monkeys, it may be inferred that the agglutinin titer for the colon group is depressed during the acute stage of the disease.²⁷

The idea that the enteric organisms have some part to play in the production of this disease was further bolstered by the fact that the monkeys which had been actively immunized had a definite, though incomplete, non-specific protection, since a longer time interval elapsed before the protected animals contracted the disease.²⁸

Other things point to the fact that the resident enteric bacillus, whether paratyphoid A or B, or some form of colon organism, may be a secondary

factor in the cause of this infection. The fact that the glands of the mesentery are enlarged is not an evidence of a general infection, but may merely indicate that the area of the intestine that they drain is involved, as would be expected in a stasod gut.

There is a lymphocytic reaction and a response in the glandular elements that is typically of a typhocoli nature. A distinct leukopenia and a relative lymphocytosis would be the expected result from an infection caused by such a close generic relative of the typhoid organism, as the colon or the paratyphoid bacillus. Such a blood picture in poliomyelitis has been described by Muller,²⁹ Taylor³⁰ and Gay and Lucas,³¹ though the figures of the latter have not been completely accepted by Peabody, Draper and Dochez.³² The most complete and accurate observations on the blood count in experimental poliomyelitis have been those made by Harmon, Shaughnessy and Gordon.³³ They reported that in the stage of prostration there is always a marked drop in the white cell count to a point far below the normal for a given animal, a leukopenia with both lymphocytes and polymorphonuclear neutrophilic leukocytes participating. They could not confirm the opinion that a change in lymphocytes with a leukopenia was a characteristic experience in the stage prior to the appearance of paralysis. In most of their experimental animals, there was a preparalytic increase in neutrophilic leukocytes coincident with a rise in body temperature and a corresponding drop in circulating lymphocytes, a drop frequently of sufficient magnitude to mask the leukocytosis when only the total number of white cells was observed. An initial transient leukocytosis was noted by these authors within a few days after the injection of the virus. I have been able to confirm these findings in duplicate studies.³⁴ During the latter stages of the disease, the lymphocytes seem to be withdrawn from circulation. This would fit in well with the advent of local intestinal stasis with the accumulation of intestinal toxins.

Osler's observations that a state of poliomyelitis occurred in typhoid fever with the symptoms of acute ascending paralysis are pertinent to our point.³⁵

Other suggestive evidence lies in the consideration of morbidity curves of infantile paralysis in relation to season. When these curves were studied, it was found that they may be practically superimposed on dysentery curves.³⁶ Aycock and Eaton³⁷ have described a spring and summer peak of poliomyelitis morbidity and have noted that the curves occur about the same time as do those for the spring and fall epidemics of typhoid fever.

In China with its teeming millions, where dysentery and gastrointestinal diseases abound, but one case of poliomyelitis was reported in Peiping Union Medical College Hospital among 25,000 admissions. In the southeastern part of the United States where gastrointestinal diseases are more common, the disease is not so prevalent though it is not entirely absent. It is a disease which is more apt to be found in those countries of the globe where dysentery or gastrointestinal diseases are not a very common factor in the weekly morbidity and mortality reports.

From the facts related, one could surmise that a dual condition of immunity may exist against this disease in the human. One person may have a high degree of protection against the gastrointestinal group of organisms and their toxins, and even though the virus is taken into the gastrointestinal tract, the individual may never become ill with the disease. On the other hand, another person may be sensitive to the typhoid-paratyphoid or to the colon bacillus factor, but immune to the virus, and thus never contract the disease.

This explanation of the mechanism of the production of poliomyelitis in the human, based on anatomical, pharmacological and experimental evidence, is one that is essentially consistent with all the vagaries of the disease.

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GASTRIC DIGESTION

A SIMPLE VISUAL TEST, AND IN VITRO STUDIES *

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UNTIL we arrive at a stage where foods may be concentrated and sufficiently predigested to allow of administration to human beings in very small quantities, studies of digestion will continue to be of extreme importance. Protein digestion is the outstanding function of the stomach, but the uncertainty and incompleteness of our knowledge concerning gastric function are attested to by the variety and multiplicity of tests for evaluating gastric digestion. These are familiar to everyone interested in gastrointestinal function, and do not need reiteration.

Some years ago, it became apparent to the senior author that the usual clinical methods of evaluating gastric digestion were far from satisfactory. The work of Schmidt¹ seemed to offer a more promising approach to this problem than any of the other procedures in use. The method of this investigator consisted in administering to the patient small gauze bags containing ground beef muscle and spleen. These bags were subsequently recovered in the stool, following which the contents were stained with methylene blue and examined microscopically. The extent of gastric digestion was determined by the intensity of the action of pepsin-HCl on the connective tissue binding the muscle fibers, while the pancreatic or tryptic digestion was indicated by the extent of dissolution of the transverse striae of the muscle fibrils and the nuclei of the sarcoplasm and splenic cells.

For some time it has been the experience of one of us (M B L) that this microscopic method of estimation of gastric function (digestion) is superior to the variable gastric analyses for routine diagnostic work. The progress of improvement or retrogression of digestion under the influence of oral administration of pepsin and acid could be well followed by this method. However, certain suppositions made by Schmidt concerning the secretions involved in the digestion of the various tissue elements present in the test meal have been found to be erroneous. In the course of investigations on this point, certain other observations of interest concerning digestion have been made.

Clinically, it has been noted consistently that administration of pepsin-hydrochloric acid to patients with subnormal digestive capacity caused the digestion of the connective tissue binding the muscle fibers, as stated by Schmidt. In addition, however, it was found that the nuclei also were completely dissolved, while even more striking was the complete obliteration of the cross-striations of the muscle fibrils when gastric function was thus restored to its normal level. In view of the fact that the microscopic esti-

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mation of gastric function is dependent upon the type of elements attacked as well as the degree of the digestion, it seemed an important point to attempt to confirm these observations under conditions more easily controlled than those prevailing in the animal body. Tests were carried out *in vitro*, with various combinations of gastric secretions in the form of scale pepsin and intestinal secretion in the form of pancreas-bile (combination) along with HCl. The action of these materials was tested on representative types of muscle tissues, including those of beef, pig, fish, fowl and crustacean. The results obtained in some of these tests are indicated in table 2.

Several points of interest resulted from the observations shown. The fact that the nuclei and the striae of the muscle tissues were visibly as well digested as the connective tissue by the pepsin-HCl alone is shown in accompanying photographs. The complete inactivity of the intestinal secretion alone on these elements is likewise illustrated, and offers a striking comparison to the activity of the gastric enzyme. Figure 1*a* illustrates partial digestion of the muscle fiber of a dried beef preparation by the action of pepsin-HCl for 120 hours. In figure 1*b* the striae and nuclei are seen to be almost completely digested, while in figure 1*c* these elements are completely digested. As contrasted with this, figure 1*d* illustrates the result of exposure to the intestinal secretion alone for 120 hours, and as demonstrated, the fiber is not affected in any way so far as the striae are concerned. The nuclei also were unaffected, but were not visible because of the lack of enzymatic action on the striae. This point has been proved by addition of pepsin-HCl to tubes containing pancreas-bile (combination) which had been totally ineffective after 96 hours. Following the addition of the gastric ferment, the striae were obliterated and the heretofore untouched nuclei became visible during the period before they too were destroyed. As expected, neither pepsin nor HCl alone exerted any action on the muscle fibers. It is evident, therefore, that pepsin-HCl in combination is the sole digestant of these elements.

As a routine procedure in the clinical application of these results, an arbitrary basis has been chosen for the expression of the degree of gastric digestion. A count is made of the relative numbers of completely digested muscle fibers, i.e., those in which the striations are absent (nuclei, of course, are not seen in stool specimens) and of the undigested fibers, which have retained their original markings. The proportion is then indicated in terms of per cent of digestion. Thus

- 100 per cent digestion—all fibers digested, as in cases of hyperacidity
- 80 per cent digestion—digested to undigested fibers in the ratio of 80:20. As the result of observations on many patients, this is considered the normal level of digestion
- 10 per cent digestion—indicates practically an anacidity. The allowance of one digested fiber out of 10 is made to cover the accidental factor involved in microscopic work

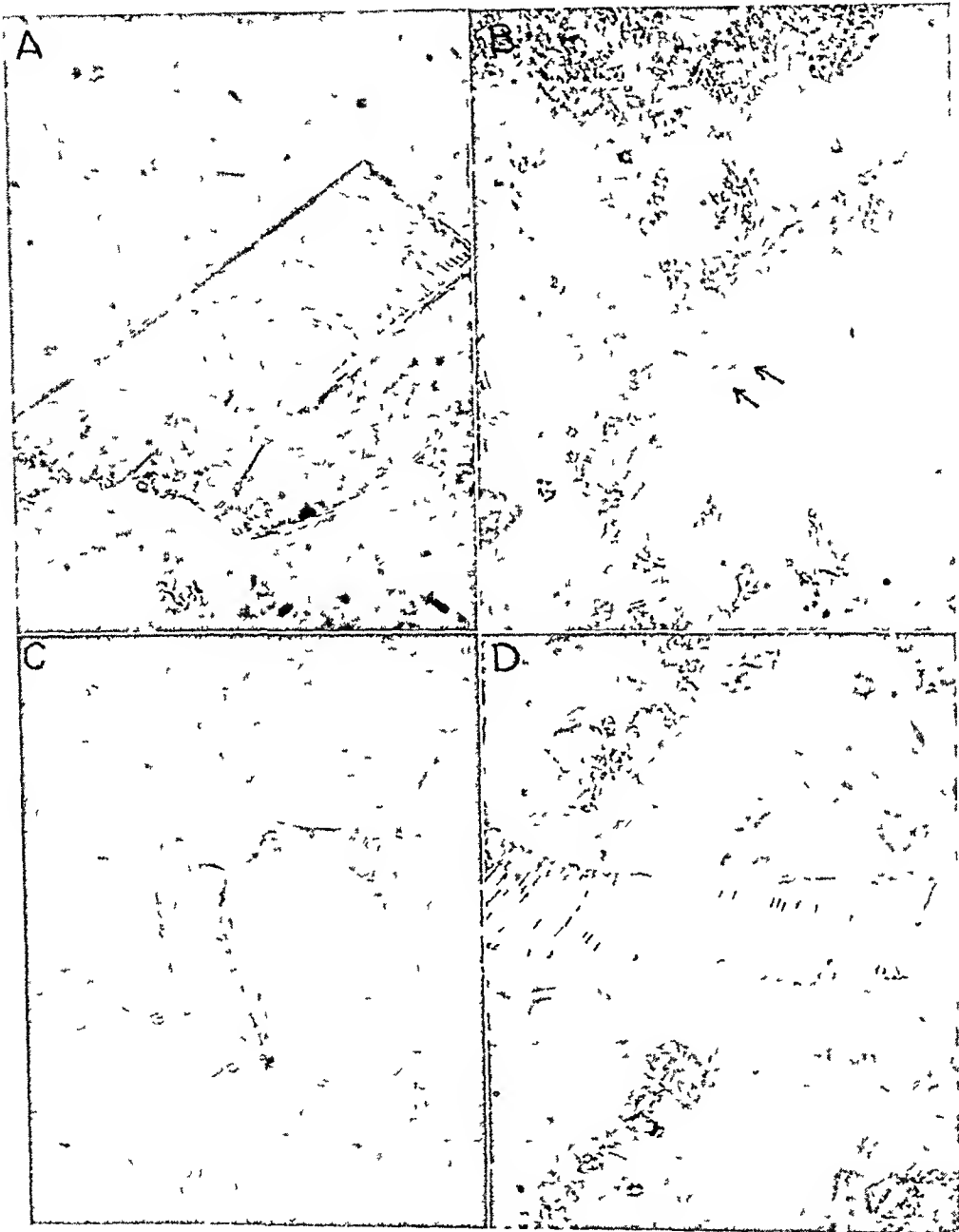


FIG 1 Digestion of powdered beef by pepsin-HCl in vitro (a) Partial fiber digestion after 120 hours (b) Partially digested striae and swollen nuclei (c) Complete digestion of striae and nuclei (d) Beef in intestinal secretion (pancreas-bile combination), undigested

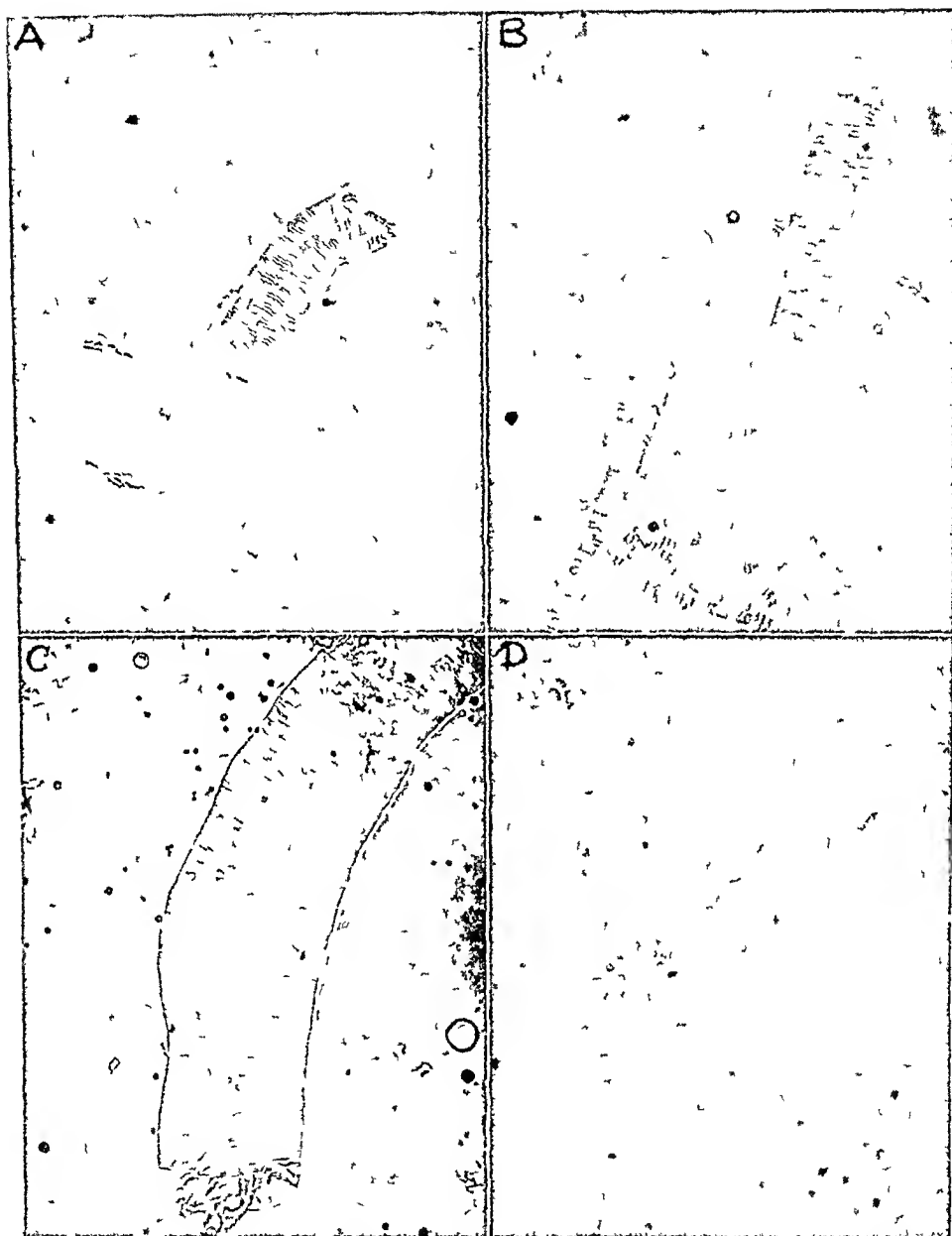


FIG. 2. Digestion of fish fiber and crab fiber in vitro. (a) Crab fiber after 120 hours in pancreas-bile combination, with Na_2CO_3 . (b) Crab fiber after 120 hours in pepsin-HCl. (c) Fish fiber after 72 hours in pancreas-bile combination with Na_2CO_3 . (d) Fish fiber after 72 hours in pepsin-HCl.

In the use of any set of values which the clinician may choose as a matter of personal convenience, account must be taken, of course, of these fibers which show only partial digestion. After some experience with the method, however, it will be found that such intermediate stages may be averaged with the completely digested and undigested forms with little difficulty. After a short period of observation, the physician may readily determine the degree of gastric digestion for practical purposes without the necessity of recourse to the stomach tube, with its attendant disturbances of the functional normality due to anticipation of the test.

In table 1 are given typical case reports illustrating the relationship between the values obtained in gastric analyses and the extent of digestion indicated by the microscopic method of stool examination.

TABLE I

| Name | Free HCl | T A | G I Meat Digestion |
|------|----------|-----------|--------------------|
| N B | 0° | 4° | 10%< |
| S C | 0° | 4° and 6° | 10%< |
| L A | 18° | 34° | 50% |
| I S | 24° | 51° | 80% |
| C E | 66° | 82° | 90%> |
| S S | 55° | 80° | 90%> |

A striking fact which appeared during the course of the work, summarized in table 2, was that under certain conditions, mixtures of gastric and duodenal secretions showed definitely better digestive abilities than either of these factors alone. This increased activity was manifested not so much as a more extensive digestion, though this was increased in most cases, but rather as a much more rapid process than that obtained with pepsin-HCl. Tubes 4 and 5, table 2, illustrate this point. The question arose as to whether the difference in action between these tubes and tube 1 (pepsin-HCl) was due to the enzymatic constituents present in the former, or to the difference in pH between the tubes. Menten, quoted by Howell,² obtained a pH of 1.0 for normal gastric juice, using hydrogen gas electrodes. Experiments by other investigators have shown, however, that an acidity this high is not favorable for the digestive action of pepsin. Thus, Michaelis and Davidsolin have stated that the optimum acidity for peptic action is at pH 1.6, when the HCl is combined in the stomach, the pH is 3.0, and at this concentration, the digestive action of pepsin is relatively feeble. As shown in table 2, the pepsin-HCl mixture was at a pH of 0.9, whereas tubes 4 and 5 were at pH 1.2 and 2.9 respectively. It was considered an important possibility that this difference in acidity might of itself account for the variation in digestive activity by the pepsin, regardless of the other enzymatic constituents of the tubes. Furthermore, it is generally thought that normal peptic activity is counteracted on contact of the gastric and duodenal contents, either in the normal manner or by regurgitation of duodenal contents into the stomach. For these reasons, further experiments were undertaken.

TABLE II
Action of Gastric and Intestinal Secretions Alone and in Combination on Muscle Fiber

| tube | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|--|-----------|----------------------|------------|-------------------------|--|---|--|--------------------------------------|---|
| Digestive enzymes in tube | | Pepsin † + HCl | Pepsin | Pancreas Bile (comb) | Pepsin + HCl + Pancreas Bile (comb) | Pepsin HCl + Pancreas- Bile (comb) Na ₂ CO ₃ | Pepsin + Pancreas Bile (comb) | Pancreas- Bile (comb) + HCl | Pancreas Bile (comb) + Na ₂ CO ₃ |
| pH* | | 0.9 | 3.5 | 7.3 | 1.2 | 2.9 | 4.9 | | 10.11 |
| Muscle fiber used and extent of digestion microscopically | Beef | 70% 50% | 20% 10% | 0 0 | 90% 60% | 90% 40% | 20% 10% | 0 0 | 0 0 |
| | Powd beef | 75% | 35% | 0 | 90% | 70% | 50% | 0 | 0 |
| After 2 1/2 hrs | | | | | | | | | |

* pH determined by quinhydrone electrode method

† It was noted that the activity of the pepsin-HCl depended upon its quantitative combination. Variation of the pepsin, of the HCl, or of the meats within limits altered the rapidity and degree of digestion. Clinically, it was found that beef up to 2 1/2 times the quantity normally given was digested to the same degree (50%, 60%, etc.) as the average amount, as determined by stool examination, indicating that the reaction to an increased demand for gastric secretions is quantitative rather than qualitative.

to determine the effect of the hydrogen-ion concentration on the digestive activity of these combinations. In table 3 are shown tubes containing different mixtures of enzymes, acid, and muscle fiber, neutralized with Na_2CO_3 , at intervals before and after contact with the various meat fibers tested.

The results recorded surprisingly demonstrated that duodenal content on contact with the pepsin-HCl immediately activated peptic digestion to a striking degree, with a rapidity several times that shown by the pepsin-acid alone. This was true when the pepsin-HCl was mixed with duodenal secretion and the test meat before neutralization (to pH of 7.0) with Na_2CO_3 , which was carried out 15 minutes later as shown in tube 6. On the other hand, if neutralization of the pepsin-HCl and pancreas-bile (combination) was carried out immediately before the meat was added, digestion was very greatly reduced. Almost no digestion at all was obtained if the pepsin-HCl was neutralized before being combined with the pancreas-bile (combination) and meat. It is thus seen that if contact was permitted between pepsin-HCl and pancreas-bile and the meat for even 15 minutes, then complete neutralization was almost wholly ineffective in curtailing the digestive activity. As shown in table 2, pepsin and pancreas-bile (combination) alone were inactive. Work on individual intestinal factors causing activation is now in progress.

It is very interesting and suggestive to attempt an application of these *in vitro* observations to the conditions existing in the gastrointestinal tract. Abderhalden and Meyer³ quoted by Hawk (Sixth Edition, page 142), have shown active pepsin to be present in the contents of all parts of the small intestine. It is suggested that pepsin may be adsorbed in the stomach by such protein substances as pass into the intestine in solid form and that the pepsin thus protected may bring about gastric digestion whenever the reaction of the surrounding intestinal contents is favorable. This fact may be of importance in connection with the profound proteolysis taking place in the intestine. Heretofore this process was believed to be furthered by trypsin and erepsin alone. Furthermore, the immediate activation of digestive activity by the contact of the gastric with the duodenal secretions may offer an explanation as to one of the chief reasons why duodenal ulcer, a condition in which there is usually a gastric hyperacidity, is found so much more commonly than gastric ulcer. It may also offer an explanation as to why certain types of operations for duodenal ulcer, which permit the free admixture of gastric and duodenal contents, may in a number of instances be ineffective as regards cure, and even permit the formation of additional postoperative ulcers at the site of operation. In addition, from the medical standpoint of treatment for gastric and duodenal ulcer, the findings presented in table 3 would indicate that unless the pepsin-HCl is neutralized completely before combining with the duodenal content, digestion of the ulcer would not be prevented sufficiently to allow healing to take place. Methods of treating gastric and duodenal ulcers might be modified to take care of these facts to a better degree than is now the case under the Sippy

TABLE III
Effect of pH on Action of Gastric and Intestinal Secretion on Muscle Fiber

| Tube | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|--|-------------|-----------------------------------|--|--|---|---|---|---|---|-----------------------------------|
| Digestive enzymes in tubes | Pepsin-HCl | Pepsin-HCl + Pancreas-Bile (comb) | Pepsin-HCl + Pancreas-Bile (comb) added after 30 minutes | Pepsin-HCl + Pancreas-Bile (comb) added after 75 minutes | Pepsin-HCl + Pancreas-Bile (comb) added after 15 minutes then neutralized | Pepsin-HCl + Pancreas-Bile (comb) (mixture neutralized with Na ₂ CO ₃ after 15 minutes) | Pepsin-HCl + Pancreas-Bile (comb) neutralized immediately | Pepsin-HCl + Pancreas-Bile (comb) neutralized immediately | Pepsin-HCl (neutralized after 15 minutes) | Pepsin-HCl + Pancreas-Bile (comb) |
| Time of addition of beef to tubes | immediately | immediately | immediately | immediately | immediately | immediately | Beef added after Pancreas-Bile (comb) and before neutralization | Beef added immediately after neutralization | immediately | immediately |
| pH of mixtures* | 0.9 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 0.9 | 4.9 |
| Results (per cent) after 24 hour digestion | 70% | 90% | 80% | 70% | 30% | 50% | 0 | 0 | 20% | 10% |

* pH determinations by quinhydrone electrode method. The pH's given in the circles where neutralization was carried out refer to the acidity before such treatment.

treatment, or the Leube, Lenhartz or other methods of treating ulcers, which have a limited percentage of success. It seems suggestive from the experiments reported that neutralization of the gastric content by means of potential or active alkalies before combination with any foods is essential for the prevention of digestion of the gastroduodenal content as well as of the duodenal wall, since even 15 minutes of exposure to gastroduodenal secretions at the proper pH is sufficient to allow a certain degree of digestion of both. Recently, one of us (M. B. L.) has carried out this procedure in the treatment of active duodenal ulcers, and the results thus far have been gratifying. The method consists in the administration of potential alkalies such as powdered CaCO_3 *just before feedings*, and of other alkalies after the meals, so that they may be "on hand" for neutralization of the secretion as manufactured as well as for subsequent neutralization of any later excess. This treatment may be employed in conjunction with any of the usual therapeutic measures employed in this condition. Doses of $1/2$ to 1 drachm of alkali are administered before the meal, in addition to the usual doses of alkalies after feeding. Digestion of meat fibers, as demonstrated by our method of stool examination, is limited to 10–20 per cent, alkalies being raised or lowered as desired through this microscopic means of control.

In conjunction with the work reported, it was decided to extend the studies of digestion to include a point which is of much clinical interest to the gastro-enterologist. In the human being, animal protein is much more readily digested than the proteins of vegetables. Unpublished data of the senior author point to such a conclusion, and Munk⁴ has shown that whereas the easily digestible animal foods are absorbed to the extent of 97 to 99 per cent, the utilization of vegetable foods is less complete. This difference is ascribed to the presence of the indigestible cellulose in vegetable foods, rather than to any peculiarities of the proteins. Recently, the same conclusion has been drawn by the British experts of the Interallied Scientific Food Commission.⁵ It was thought that since in certain conditions, such as esophageal carcinoma, a conveniently administered and easily digested form of animal protein is highly desirable, a comparative *in vitro* and *in vivo* study of the digestion of various types of meats would be profitable. For this purpose, cooked fish, beef, pork, lamb, veal, crab, and chicken were used. In addition, a preparation of powdered beef^{*} containing 10 per cent powdered liver, ground celery seed, and the salts of calcium, magnesium, sodium, potassium, etc., added in quantities to bring these elements to the level of the normal requirements, was used.

In the stools of individuals with normal digestive ability, it has been found that non-oily types of cooked fish were most easily digested, the preserved type of bacon and fried or cooked crab were most difficult to digest, while beef and fowl occupied intermediate positions of digestibility. The results obtained in test tube experiments may be seen in figures 1 and 2, which are representative examples of the action of pepsin-HCl on these

^{*} This preparation was furnished through the cooperation of the experimental department of the Valentine Meat Juice Corporation of Richmond, Va.

cooked fibers The crab is shown before digestion and after 120 hours in pepsin-HCl at room temperature, it will be noted that only partial digestion has occurred Under the same conditions, the fish is seen to be completely digested, as is also the powdered beef

Since the dried beef-liver was found to undergo digestion as well as ordinary cooked beef, this preparation has been put to practical use in various types of cases with very satisfactory results Suspended in water, bouillon or other liquid vehicles it has been injected through a duodenal tube with syringe, without fear of blockage In cases where difficulty was experienced in swallowing lumpy masses due to throat affections or following tonsillectomy or tooth extraction, in infants and children when a convenient form of beef easily administered in a fluid medium was required, in forced feeding cases, and in adults or children in whose diets carbohydrates and fats could not be raised, but in whom an increase of bulky proteins beyond a certain quantity was nauseating, this preparation has been successfully employed

SUMMARY AND CONCLUSIONS

1 A microscopic method of estimation of gastric digestion based on the demonstrated ability of the gastric secretions to digest striae, connective tissue and nuclei, has been found to furnish a satisfactory index of gastric function (digestion)

2 The mixture of secretions derived from the duodenum when combined with pepsin-HCl promotes the rapidity of digestion to a marked degree Such increased activity occurs if the components are allowed to act on the test material at an appropriately low pH Under these conditions, neutralization of the acid after a short period inhibits the progress of the digestion to some degree only When neutralization of the mixture is effected before it has come into contact with the test material, however, no digestive activity is manifested On the basis of these observations, it is suggested that large doses of alkali be administered both before and after meals in cases of duodenal ulcer

3 Simultaneous experiments on the comparative digestibilities *in vivo* and *in vitro* of various animal proteins in the form of representative meats have indicated that a dried beef-liver preparation is of value in cases where such proteins are desired but cannot be conveniently taken in the usual manner

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EDITORIAL

PHYSIOLOGICAL AND CHEMICAL RELATIONSHIPS OF THE SEX HORMONES

ALMOST all of our chemical and physiological knowledge of the estrogenic hormone has been acquired within a decade. Credit for this progress belongs to many workers. The stimulus which has produced such rapid development was furnished primarily by important studies. One was reported by Allen and Doisy late in 1923 when they showed that the injection of alcoholic follicular extracts from hog ovaries would bring about estrus in castrated mice or rats¹. The second advance was made by Aschheim and Zondek in 1927,² when they demonstrated a substance in the urine of pregnant women which conformed in all of its biological effects to the material found earlier in the follicular fluid. This discovery opened up the way to productive chemical investigation, because it pointed to an abundant source of the material, which was free of proteins and lipoids, thus greatly facilitating the work of extraction. In 1929 its isolation in crystalline form was announced by Doisy³ and almost simultaneously by Butenandt⁴.

The essential chemical configuration of the female sex hormone is that of a condensed carbon ring compound composed of three six-membered rings, together with a five-membered ring attached at one end. It is a derivative of phenanthrene. The condensed carbon ring compounds, as sterols, occur also in cholesterol and its derivatives, the bile acids, as well as in ergosterol, and hence, in vitamin D. As is now believed, the same essential characteristic structure also occurs in the closely related male sex hormone as well.

The clinical value of the estrogenic hormone has not been seriously regarded up to the present time. Certain reports made almost within the year may now serve to change this attitude materially. It appears that rather large amounts of the material, which have not been obtainable until very recently, are necessary to bring about clinical effects in woman. Kaufmann has recently reported that menstrual changes can be produced in the castrated woman with a dose of approximately one million rat units⁵. Much larger doses, five-fold, spread over a period of weeks, will produce an actual glandular cystic hyperplasia. This work, which has in part been confirmed in England, was rendered possible by the interesting discovery that a com-

¹ ALLEN, E., and DOISY, E. A. Ovarian hormone, preliminary report on its localization, extraction and partial purification, and action in test animals, *Jr Am Med Assoc*, 1923, **LXXXI**, 819-821.

² ASCHHEIM, S. and ZONDEK, B. Hypophysenvorderlappenhormon und Ovarialhormon im Harn von Schwangeren, *Klin Wchnschr*, 1927, **vi**, 1322.

³ DOISY, E. A., THAYER, S., and VILER, C. D. Preparation of crystalline ovarian hormone from urine of pregnant women, *Jr Biol Chem*, 1930, **LXXXVI**, 499-509.

⁴ BUTENANDT, A. *Naturwissensch*, 1929, **xvii**, 879.

⁵ KAUFMANN, C. Therapeutics with hormones of ovary, *Proc Roy Soc Med*, 1934, **LXXII**, 849-863.

pound elaborated synthetically from the hormone itself, by the addition of two atoms of hydrogen will increase its activity several fold⁶ If further hydrogen atoms are added, the compound loses its estrogenic activity, and if six more be attached, it is said, it develops properties of the male sex hormone

The strict specificity of the female sex hormone has been rendered dubious, indeed, in the light of several lines of investigation It has been known for some time that certain vegetable extracts possess the property of provoking estrus in rodents exactly as does the estrogenic hormone⁷ Conversely, a few milligrams of crystalline folliculin when placed in water surrounding hyacinth bulbs will hasten remarkably the floral development⁸ Butenandt, again, has demonstrated the identity of the phytohormone derived from palm fruit, and obtained in crystalline form,⁹ with the estrogenic hormone Another group of compounds with estrogenic activity was produced last year by Aschlheim and Hohlweg,¹⁰ who used coals, asphalt and petroleum oils as their starting point They made the ingenious suggestion that the substance in coal might be the variety of the estrus hormone known to be present in plants, and suggested that it originated in the primeval, coal producing forests Dodds¹¹ and Cook and their associates last year reported studies on compounds derived from phenanthrene which is obtained from coal tar These differ in structure from the natural estrogenic substances in the absence of the attached five carbon ring, but at least one member of the series of derivatives studied possesses even greater potency than one of the natural estrogenic agents recovered from pregnant urine Not only are these observations of great general interest, but they possess practical therapeutic potentialities as well In two instances these compounds have been shown to have besides their estrus-producing power, another characteristic property of the naturally occurring sex hormone, namely, that of causing a reversion of the plumage of the brown leghorn capon to the female type So far as is known, these somewhat simpler compounds, differing materially from the natural estrus-producing hormone, possess all of the known types of activity of the latter Such observations cast doubt on the specificity of this natural hormone and may offer a better explanation of the origin of the active substances derived from bitumens Substances producing tar cancer have also a related structure and in one or two instances also have been shown to have feeble estrogenic activity¹¹

Finally vitamin D is also a member of the condensed carbon ring group

⁶ SCHWENK, E and HILDEBRANDT, F *Naturwissensch* 1933, xxi, 177

⁷ LOFWE S LANGF, F and SPOHR, E Über weibliche Sexualhormone (Thelytropine), brunsterzeugende Stoffe (Thelykinine) als Erzeugnisse des Pflanzenreiches, *Biochem Ztschr*, 1927 cxvii 1-26

⁸ SCHOELLER, W and GOEBEL, H Die Wirkung des Follikelhormons auf Pflanzen, *Chem Ztschr*, 1931 cxvi 1-11

⁹ GIRARD, A *Bull Soc Chim Biol* 1933, x, 581

¹⁰ ASCHLHEIM, S, and HOHLWEG, W Über das Vorkommen oestrogenen Wirkstoffe in mittel, *Deutsch med Wchnschr* 1933, lv, 12-14

¹¹ MUNK, I E C Hormones and their chemical relations (Goulstonian lecture), *Lancet*,

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of compounds, and a study of several sterols allied to ergosterol has shown these to have estrus-producing properties, most marked in the case of neo-ergosterol, but definite in the case of ergosterol itself, as well as in that of the closely related vitamin D ¹¹. The amount of the latter required to produce estrus is very large in relation to the amount needed to protect against rickets, but the estrus changes take place before any signs whatever are seen of hypervitaminosis. A single substance, therefore, has been shown to possess two entirely distinct physiological properties, one characteristic of a vitamin (antirachitic) and one of a hormone (estrogenic). It seems quite clear that further study of the sterol group in its relation to animal metabolism furnishes a promising field not only for advancing knowledge of the mechanism of vitamin and hormone action, but for the discovery of compounds of possible therapeutic value as well.

GEORGE A. HARROP

REVIEWS

The Compleat Pediatrician Practical, Diagnostic, Therapeutic and Preventive Pediatrics By WILBURT C DAVISON The Duke University Press, Durham, N C 1934 Price, \$3.75

Here is a book out of the ordinary which starts out with a clever adaptation of the title page of Isak Walton's *Compleat Angler*. The author was for some time the acting pediatrician to the Johns Hopkins Hospital and now fills the chair at Duke University. It is a book primarily for the medical student and the busy practitioner, and it has been kept small enough to be put in the bag of the pediatrician along with such necessities as the stethoscope and otoscope. It is divided into various parts setting forth the signs and symptoms, the various diseases, the laboratory tests, the preventive measures and the treatment and prognosis.

If the student knows the principal signs and symptoms he may, by consulting the book, find out in which conditions they are found and then, by using the cross references, learn what is to be done to prevent or cure. There are numerous tables showing the development of the child, diagnostic aids, foods, drugs and what not so that in one small volume one may have the cream of pediatric knowledge, very much condensed it is true, but all there. The amount of labor which went into the making of this book was certainly very great, it occupied the spare time of eight years, and well it might. Only those with encyclopedic memories can call to mind the many details which are in daily use. This book will help those of us who are not so endowed.

Among other things we learn that of the 307 diseases to which children are heir, only 100 are important, that is the 37 which cause 56 per cent of the deaths in children and which are preventable, and the 63 which are responsible for 21 per cent of the pediatric deaths and which respond to adequate therapy. One may question placing allergy and epilepsy in this group. When the author adds automobile accidents and suggests teaching children at home or if they are in school to take constant precautions one has to smile. Nevertheless the book is a real contribution and may be recommended most highly for just what it claims to be, a help to the student and to serve as a *vide mecum* for the practitioner. The author is to be congratulated.

J H R

Medicine in Canada Cho Medica Series By WILLIAM BOYMAN HOWELL, M D
viii + 137 pages, 11.5 x 17 cm Paul B Hoeber, Inc, New York 1933
Price, \$1.50

Canada has had several medical historians of note including J J Haegerty, H S Birkett, M R Charlton and Maude E Abbott, and now comes Howell with this little volume in the Cho series. Starting with Jacques Cartier and his experience with scurvy which happened in 1535 the author comes down through the years at a rather startling pace and winds up about 1870, using short chapters either biographical or regional. It seems a pity that he did not add a few pages and bring it down to date, or a history of medicine in Canada without the name of Osler in it seems an oddity. We were brave days when Bonnerme, surgeon to Champlain, narrowly escaped being hanged for having been implicated in a plot to kill the leader. The plotters were rehended while trying to decide whether they should shoot or strangle him.

MURK I'ing little book

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J H R

Davis' Applied Anatomy Ninth Edition By GWILYM G DAVIS, M D revised by GEORGE P MULLER, M D 717 pages, 26.5 × 19 cm J B Lippincott Co, Philadelphia 1934 Price, \$9.00

This book, in its ninth revision since 1910, needs no new recommendation. The present edition preserves the excellent form and typography of the old, and many sections have been entirely rewritten. The author of this revision, Dr George P Muller, has been assisted by several surgical specialists all of whom have maintained a high standard in their various sections. Eighty-six pages have been added which are chiefly devoted to the applied anatomy of special surgery. There are also many new illustrations.

In the light of the general excellence of this edition, the reviewer hesitates to mention occasional errors in labeling, such as are seen in distinguishing the inguinal fossae, on page 441, and the omission of a designation, on page 443. The description of the fascial spaces in the hand might also have been enlarged upon to advantage.

The subject matter is, as in other editions, a very good example of the use of mature judgment in selecting the material which fills the gap between anatomy and surgery.

E M H, Jr

Tumors of the Female Pelvic Organs By JOE VINCENT MEIGS, A B, M D, F A C S, Instructor in Surgery, Harvard Medical School, Surgeon to Out-Patients, Massachusetts General Hospital, Associate Surgeon, Collis P Huntington Memorial Hospital, Surgeon, Pondville Hospital, Massachusetts State Cancer Hospital 533 pages, 24 × 16 cm Macmillan Co, New York 1934 Price, \$6.00

This work will be of interest to all students of medicine and particularly so to the gynecologist, pathologist and radiologist. The subject is clearly and painstakingly presented and shows the care with which the material has been evaluated.

The first five chapters deal with carcinoma of the cervix and carcinoma of the body of the uterus and the excellent presentation of this phase of the work follows the general plan carried out in the remaining chapters.

First, there is a general discussion of the subject which is followed by the pathology of the tumors of each organ and to this is added the symptomatology manifested by the lesion. The author then presents a statistical report of his series of cases which, although small in number, are of value due to the thoroughness with which they have been studied. The methods of treatment, especially by radium and x-ray, are clearly presented in detail. The author correctly states that there are two methods of treating cancer of the cervix, surgery and radium, and that in all but the very early cases surgery should be abandoned. He further states that this study has shown that surgery will cure some cases of carcinoma of the cervix with lymph node involvement and there is reason to believe that radium will not. This latter statement is, however, debatable.

The chapter on Tumors of the Ovary, comprising 110 pages, is well presented. The text is clear, easily readable, and the illustrations are good. The section on embryonal tumors, including the feminizing and masculinizing group, is of particular interest.

The final chapter devoted to metastases occurring throughout the body, chiefly from the cervix, body of the uterus, and the ovary, is most instructive.

At times the text is prolix, due to repetition, but in such a statistical study this is difficult to avoid.

The book is well worthwhile and the correlation of the accumulated knowledge of the tumors of the female pelvic organs in regard to pathology, clinical symptoms and treatment fills a decided need.

J M H

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members

- Dr Herbert Thomas Kelly (Fellow) and Dr J T Beardwood, Jr (Fellow), Philadelphia, Pa—one book, "Simplified Diabetic Management"
Dr Thurman D Kitchin (Fellow), Wake Forest, N C—one book, "The Doctor and Citizenship"

Acknowledgment is also made of the receipt of reprints from the following

- Dr J Reid Broderick (Fellow), Savannah, Ga—1 reprint,
Dr Alvin G Foord (Fellow), Pasadena, Calif—12 reprints,
Dr W E R Schottstaedt (Fellow), Fresno, Calif—2 reprints,
Dr John W Shuman (Fellow), Los Angeles, Calif—1 reprint,
Dr Ramon M Suarez (Fellow), San Juan, Puerto Rico—3 reprints,
Dr Willard J Davies (Associate), Rockville Center, N Y—1 reprint

Dr Julius H Comroe, Sr (Fellow), York, Pa, has been elected to membership upon the Scientific Advisory Board of the American Medical Editors' and Authors' Association, to serve one year, beginning January 1, 1935 Dr Dean Lewis, Baltimore, Md, has been elected President

Dr Henry K Taylor (Fellow), has been appointed to the teaching staff of the New York University for the academic year 1934 to 1935 as Instructor in Radiology by the Council of that University

The Southeastern Surgical Congress, through its Secretary, Dr B T Beasley, announces the Sixth Annual Assembly of the Congress, which will be held in Jacksonville, Fla, March 11, 12 and 13 1935 The Congress has met previously in Atlanta, Birmingham and Nashville The States composing the Congress are Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee and Virginia Many distinguished surgeons will appear on the program, which will be completed about February 15, 1935 Interested physicians may address Dr B T Beasley, Secretary-Treasurer, 1019 Doctors Bldg, Atlanta, Ga

The Los Angeles County Heart Association held its Third Annual Symposium on Heart Disease on December 6 and 7, 1934 Dr A S Granger (Fellow) and Dr William H Leake (Fellow) are President and Secretary-Treasurer, respectively The following Fellows of the College contributed to the program

| | | |
|---------------------|---------------------|-------------------|
| Dr E Richmond Ware | Dr A S Granger | Dr Roy Thomas |
| Dr Willard J Stone | Dr Newton Evans | Dr F M Pottenger |
| Dr Egerton Crispin | Dr D D Comstock | Dr Donald J Frick |
| Dr John C Ruddock | Dr B O Raulston | Dr Harold H Smith |
| Dr William H Leake | Dr Wm C Boeck | |
| Dr Arthur M Hoffman | Dr R Manning Clarke | |

Dr William Gerry Morgan (Fellow and Secretary-General of the College), Washington, D C, was named by the Commissioners of the District of Columbia to head a committee for the selection of a new Health Officer for the District of

Columbia The Committee laid down 15 requisite qualifications for candidates, and has thoroughly investigated the best nominees. The position pays \$7,000.00 per annum, and it is expected the candidate will have been elected by the time this announcement is printed.

ELECTIONS TO THE COLLEGE

At a regular meeting of the Board of Regents of the American College of Physicians at the headquarters in Philadelphia, December 16, 1934, the following elections to Fellowship and Associateship were made. After each candidate's name, "1" indicates the name of the proposer, "2" indicates the name of the seconder, and "3" indicates the name of the endorser.

Elections to Fellowship

George Albert Alden, M C, U S N, Washington, D C

- (1) P F Dickens
- (2) Lewis H Roddis
- (3) P S Rossiter

George E Baxter, Chicago, Ill

- (1) N S Davis, III
- (2) Charles A Elliott
- (3) James G Carr

A Lee Briskman, Colorado Springs, Colo

- (1) G Burton Gilbert
- (2) John A Sevier
- (3) Gerald B Webb

Albert W Bromer, New York, N Y

- (1) Thomas M McMillan
- (2) Charles C Wolferth
- (3) William D Stroud

Michael A Burns, Philadelphia, Pa

- (1) Edward A Strecker
- (2) Edward Weiss
- (3) E J G Beardsley

Horace W Carle, St Joseph, Mo

- (1) L H Fuson
- (2) P T Bohan
- (3) A C Griffith

Fred Ellsworth Clow, Wolfeboro, N H

- (1) Harry T French
- (2) H W N Bennett
- (3) Robert B Kerr

Sterling Smith Cook, M C, U S N, Washington, D C

- (1) O J Mink
- (2) Louis H Roddis
- (3) P S Rossiter

Austin Clifford Davis, Rochester, Minn

- (1) W A Plummer
- (2) George E Brown
- (3) E L Tuohy

John J Dumphy, Worcester, Mass

- (1) Peter A Colberg
- (2) George M Albee
- (3) William B Breed

Maurice F Dwyer, Seattle, Wash

- (1) Lester J Palmer
- (2) G A Dowling
- (3) Frederick Epplen

Mary Hoskins Easby, Philadelphia, Pa

- (1) James E Talley
- (2) Joseph T Beardwood, Jr
- (3) William D Stroud and E J G Beardsley

Carl Edgar Ervin, Danville, Pa

- (1) Alfred Stengel
- (2) O H Perry Pepper
- (3) Geo Morris Piersol

Hugh Allan Farris, St John, New Brunswick, Can

- (1) W E Ogden
- (2) Jabez H Elliott
- (3) D Sclater Lewis

Grant O Favorite, Philadelphia, Pa

- (1) E Roland Snader, Jr
- (2) S W Sappington
- (3) E J G Beardsley

Russell Allen Flack, La Fayette, Ind

- (1) R D Bayley
- (2) M M Lairy
- (3) Robert M Moore

Alvin George Foord, Pasadena, Calif

- (1) Willard J Stone
- (2) F M Pottenger
- (3) Egerton Crispin

Leonard H Fredricks, Bismarck, N D

- (1) H A Brandes
- (2) Paul H Rowe
- (3) Julius O Arnson

James Jackson Gable, Norman, Okla

- (1) Tom Lowry
- (2) Hugh Jeter
- (3) Lea A Rielv

Amos Carvel Gipson, Gadsden, Ala

- (1) C C McLean
- (2) Seale Harris
- (3) James S McLester

A Allen Goldbloom, New York, N Y

- (1) I W Held
- (2) Linn J Boyd and Harlow Brooks
- (3) James Alex Miller and Robert A Cooke

David Greer, Houston, Texas

- (1) M L Graves
- (2) Moise D Levy
- (3) C T Stone

George Tryon Harding Columbus, Ohio

- (1) John Dudley Dunham
- (2) E F McCampbell
- (3) A B Brower

William Walter Hargrave, M C, U S N, Washington, D C

- (1) P F Dickens

- (2) Walter A Bloedorn
- (3) P S Rossiter
- Marion Douglas Hargrove, Shreveport, La
 - (1) W S Kerlin
 - (2) Dean Hume Duncan
 - (3) J E Knighton
- Gordon Hastings, Little Rock, Ark
 - (1) F O Mahony
 - (2) H T Smith
 - (3) Oliver C Melson
- Ivan Hekimian, Buffalo, N Y
 - (1) Carroll J Roberts
 - (2) Nelson G Russell
 - (3) Allen A Jones
- Wybren Hiemstra, Missoula, Mont
 - (1) Allen Richard Foss
 - (2) Harold W Gregg
 - (3) Louis H Fligman
- Herbert Thomas Kelly, Philadelphia, Pa
 - (1) James E Talley
 - (2) Joseph T Beardwood, Jr
 - (3) E J G Beardsley
- Dunne Wilson Kirby, Philadelphia, Pa
 - (1) G Harlan Wells
 - (2) Donald R Ferguson
 - (3) Geo Morris Piersol and E J G Beardsley
- Louis I Kramer, Providence, R I
 - (1) Guy W Wells
 - (2) Charles F Gormly
 - (3) Alex M Burgess
- Eugene Markley Landis, Philadelphia, Pa
 - (1) T Grier Miller
 - (2) Charles C Wolferth
 - (3) O H Perry Pepper and E J G Beardsley
- Lowell Lefferts Lane, Philadelphia, Pa
 - (1) E Roland Snader, Jr
 - (2) Donald R Ferguson
 - (3) E J G Beardsley
- Roy John Leutscher, M C, U S N, San Diego, Calif
 - (1) Otis Burgess Spalding
 - (2) W A Vogelsang
 - (3) P S Rossiter
- Dean W Marquis, East Orange, N J
 - (1) Harvey M Ewing
 - (2) John W Gray
 - (3) Clarence L Andrews
- Alexis Tice Mays, Brooklyn, N Y
 - (1) A F R Andresen
 - (2) Eugene S Dalton
 - (3) Luther F Warren and Robert A Cooke
- Samuel James McClendon, San Diego, Calif
 - (1) Lyell Cary Kinney
 - (2) Clair L Stealy
 - (3) Egerton Crispin

- William Patton McDowell, Norfolk, Va
 (1) C L Harrell
 (2) Walter B Martin
 (3) J Morrison Hutcheson
- Ralph James McMahon, Endicott, N Y
 (1) H B Marvin
 (2) James Herbert Donnelly
 (3) Robert A Cooke
- Oliver J Menard, Springfield, Mass
 (1) Lewis M Hurvthal
 (2) Frank N Allan
 (3) Roger I Lee
- Clarence Dewey Moll, Detroit, Mich
 (1) Henry R Carstens
 (2) Alpheus F Jennings
 (3) James D Bruce
- Bradford James Murphey, Colorado Springs, Colo
 (1) G Burton Gilbert
 (2) John A Sevier
 (3) Gerald B Webb
- Sydney Nussbaum, Brooklyn, N Y
 (1) Philip I Nash
 (2) Judson P Pendleton
 (3) Luther F Warren and Robert A Cooke
- Marjorie E Reed, Plymouth, Pa
 (1) G E Baker
 (2) Edward I Wolfe
 (3) E J G Beardsley
- Floyd Leslie Rogers, Lincoln, Nebr
 (1) Geo W Covey
 (2) A L Smith
 (3) Adolph Sachs
- Edward Rose, Philadelphia, Pa
 (1) T Grier Miller
 (2) Richard A Kern
 (3) O H Perry Pepper and E J G Beardsley
- Howard A Rush, St Louis, Mo
 (1) Walter Baumgarten
 (2) Elsworth S Smith
 (3) A C Griffith
- Harold Rypins, Albany, N Y
 (1) Willard C Rappleye
 (2) Luther F Warren
 (3) Wm Gerry Morgan and Robert A Cooke
- George A Sheehan, Brooklyn, N Y
 (1) Tasker Howard
 (2) A F R Andresen
 (3) Luther F Warren and Robert A Cooke
- James Joseph Short, New York, N Y
 (1) Milton A Bridges
 (2) Walter G Lough
 (3) Robert A Cooke
- Neuton S Stern, Memphis, Tenn
 (1) J B McElroy

- (2) Otis S Wari
- (3) J Owsley Mamei
- John Augustin Sweeney, Philadelphia, Pa
 - (1) Joseph C Doane
 - (2) Arthur C Morgan
 - (3) E J G Beardsley
- Charles William Warren, Rochester, N Y
 - (1) William S McCann
 - (2) Charles B F Gibbs
 - (3) Allen A Jones
- Harvey Middleton Watkins, Polk, Pa
 - (1) W H Mayer
 - (2) A H Stewart
 - (3) E Bosworth McCready
- Ernest S Wegner, Lincoln, Nebr
 - (1) Arthur L Smith
 - (2) Geo W Covey
 - (3) Adolph Sachs
- August A Werner, St Louis, Mo
 - (1) Charles Hugh Neilson
 - (2) Augustus P Munsch
 - (3) David Barr
- James Alfred Wilson, Meriden, Conn
 - (1) Thomas P Murdock
 - (2) Cole B Gibson
 - (3) Henry F Stoll
- Charles Benjamin Wright, Minneapolis, Minn
 - (1) Walter L Bierring
 - (2) Frank W Spicer
 - (3) Edward L Tuohy

Elections to Associateship

- Kenneth Ellmaker Appel, Philadelphia, Pa
 - (1) Edward A Strecker
 - (2) Richard A Kern
 - (3) O H Perry Pepper and E J G Beardsley
- James B Berardi, Tuscaloosa, Ala
 - (1) James S McLester
 - (2) James E Paullin
 - (3) Fred Wilkerson
- Ernest L Boylen, Portland, Ore
 - (1) Homer P Rush
 - (2) John H Fitzgibbon
 - (3) T Homer Coffen
- Irving Brotman, Washington, D C
 - (1) Walter Freeman
 - (2) Tomas Cajigas
 - (3) Wallace M Yater
- Paul Douglas Camp, Richmond, Va
 - (1) Dean B Cole
 - (2) R Finley Gayle
 - (3) J Morrison Hutcheson
- T Nelson Carey, Baltimore, Md
 - (1) Maurice C Pincoffs

- (2) Louis Krause
- (3) Henry M Thomas, Jr
- Lyman Bruce Carruthers, Miraj, S M C , India
 - (1) John A Macgregor
 - (2) C M Crawford
 - (3) Jabez H Elliott
- John Richard Cavanagh, Washington, D C
 - (1) Lester Neuman
 - (2) W F O'Donnell
 - (3) Wallace M Yater
- Casimir Joseph Czarnecki, Toledo, Ohio
 - (1) C W Waggoner
 - (2) John T Murphy
 - (3) A B Brower
- T Dewey Davis, Richmond, Va
 - (1) Charles M Caravati
 - (2) Dean B Cole
 - (3) J Morrison Hutcheson
- Elbert DeCoursey, M C , U S A , Ancon, Canal Zone
 - (1) Lawrence Getz
 - (2) Lewis B Bates
 - (3) Wm M James
- Frederic Griffin Dorwart, Muskogee, Okla
 - (1) L J Moorman
 - (2) John E Heatley
 - (3) Lea A Riely
- Charles Hilbert Drenckhahn, Rochester, Minn
 - (1) E V Allen
 - (2) A B Rivers
 - (3) E L Tuohy
- Thomas Morton Durant, Ann Arbor, Mich
 - (1) Cyrus C Sturgis
 - (2) Charles L Brown
 - (3) James D Bruce
- John Sheldon Eastland, Baltimore, Md
 - (1) Maurice C Pincoffs
 - (2) Louis Krause
 - (3) Henry M Thomas, Jr
- Earl B Erskine, M C , U S N , Parris Island, S C
 - (1) C S Butler
 - (2) I W Jacobs
 - (3) P S Rossiter
- Daniel Leo Finucane, Washington, D C
 - (1) J Winthrop Peabody
 - (2) William D Tewksbury
 - (3) Wallace M Yater
- Luther Irvin Fisher, Bethlehem, Pa
 - (1) Francis J Dever
 - (2) William D Stroud
 - (3) Geo Morris Piersol
- James Hedges Forsee, M C , U S A , Denver, Colo
 - (1) E L Cook
 - (2) William C Pollock
 - (3) Robert U Patterson

Richard France, Woodbrook, Baltimore Co , Md

- (1) Thomas R Brown
- (2) Sydney R Miller
- (3) Henry M Thomas, Jr

William Freeman, Worcester, Mass

- (1) Erwin C Miller
- (2) G M Albee
- (3) Roger I Lee and William B Breed

— Sanford William French, M C , U S A , Fort Sam Houston, Texas

- (3) Robert U Patterson

Julian Carrel Gant, Melrose, Mass

- (1) Howard B Sprague
- (2) F Dennette Adams
- (3) J H Means and William B Breed

J Francis Gardiner, Omaha, Nebr

- (1) John R Kleyla
- (2) Maurice C Howard
- (3) Adolph Sachs

William Middendorf Gentlner, Brooklyn, N Y

- (1) A F R Andresen
- (2) Frank Bethel Cross
- (3) Robert A Cooke

Warren Monroe Gilbert, Boulder, Colo

- (1) Clough Turrill Burnett
- (2) R W Arndt
- (3) Gerald B Webb

Stephen A Graczyk, Buffalo, N Y

- (1) Carroll J Roberts
- (2) Francis D Leopold
- (3) Allen A Jones

William Bandy Grayson, Little Rock, Ark

- (1) F O Mahony
- (2) H T Smith
- (3) Oliver C Melson

William Hugh Griffith, Huron, S D

- (1) John L Calene
- (2) C F Morsman
- (3) S Marx White

Lewis Perkins Gundi, Baltimore, Md

- (1) Maurice C Pincoffs
- (2) Louis Krause
- (3) Henry M Thomas, Jr

Harry Halprin, Caldwell, N J

- (1) Harvey M Ewing
- (2) Harlow Brooks
- (3) Clarence L Andrews

James Fletcher Hanson, Decatur, Ga

- (1) Hal M Davison
- (2) C W Strickler
- (3) Russell H Oppenheimer

Karl J Henrichsen, Chicago, Ill

- (1) Henry C Sweany
- (2) Frederick Lice
- (3) James B Herrick and James G Carr

Edgar Schall Henry, Sewickley, Pa

- (1) Joseph H Barach
- (2) Samuel R Haythorn
- (3) E Bosworth McCready

Henry Finlay Hyndman, Wichita, Kan

- (1) Thomas T Holt
- (2) Harold W Palmer
- (3) J H Musser

Harry Julius Johnson, New York, N Y

- (1) Milton A Bridges
- (2) J Russell Twiss
- (3) Robert A Cooke

W Floyd Keller, Oklahoma City, Okla

- (1) L J Moorman
- (2) John E Heatley
- (3) Lea A Riely

Bert Fletcher Keltz, Oklahoma City, Okla

- (1) L J Moorman
- (2) Arthur B Chase
- (3) Lea A Riely

Robert Leonard King, Seattle, Wash

- (1) George Dowling
- (2) John Blackford
- (3) Frederick Epplen

Frank Hammond Krusen, Philadelphia, Pa

- (1) Edward Weiss
- (2) John A Kolmer
- (3) E J G Beardsley

Romeo J Lajoie, Los Angeles, Calif

- (1) Bertnard Smith
- (2) Howard F West
- (3) F M Pottenger and Egerton Crispin

Arthur E Lamb, Brooklyn, N Y

- (1) Joshua M Van Cott
- (2) Nathan T Beers
- (3) Luther F Warren and Robert A Cooke

Louis B Laplace, Philadelphia, Pa

- (1) Thomas M McMillan
- (2) David Riesman
- (3) W D Stroud

William Gilmore Leiman, Jr, Philadelphia, Pa

- (1) Robert G Torrey
- (2) Frank W Burge
- (3) E J G Beardsley

George Morris Lewis New York, N Y

- (1) J Homer Cudmore
- (2) Leon T LeWild
- (3) Robert A Cooke

Thomas K Lewis, Camden, N J

- (1) E J G Beardsley
- (2) Thomas M Kain
- (3) Clarence L Andrews

James M Lynch, Panama City, Panama

- (1) Lawrence Getz

- (2) C D Briscoe
- (3) Wm M James
- Paul Bernard Mason, Rochester, Minn
 - (1) George E Brown
 - (2) E V Allen
 - (3) E L Tuohy
- William R Mathews, Shreveport, La
 - (1) D H Duncan
 - (2) W S Kerlin
 - (3) J E Knighton
- Randolph L McCalla, San Francisco, Calif
 - (1) H Clare Shepardson
 - (2) William J Kerl
 - (3) H Lisser
- Edward McCloskey, Philadelphia, Pa
 - (1) Josephus T Ullom
 - (2) T Grier Miller
 - (3) Geo Morris Piersol
- John McFaul McEachern, Winnipeg, Man, Can
 - (1) J Currie McMillan
 - (2) J G FitzGerald
 - (3) Fred T Cadham
- Fred John McEwen Wichita, Kan
 - (1) Howard E Marchbanks
 - (2) Peter T Bohan
 - (3) Thomas T Holt
- Clovis Litle McKibben, Toledo, Ohio
 - (1) C W Waggoner
 - (2) John T Murphy
 - (3) A B Brower
- Roscoe Frick Millet, Rochester, Minn
 - (1) George E Brown
 - (2) E V Allen
 - (3) E L Tuohy
- Philip Wilhelm Morgan, Emporia, Kan
 - (1) Peter T Bohan
 - (2) A Morris Ginsberg
 - (3) Thomas T Holt
- Samuel Morrison, Baltimore, Md
 - (1) Julius Friedenwald
 - (2) Theodore H Morrison
 - (3) Henry M Thomas, Jr
- Carlisle Morse, Louisville, Kv
 - (1) John Walker Moore
 - (2) J Murray Kinsman
 - (3) E B Bradley
- Charles Scott Mudgett, M C , U S A , Fort Devens, Mass
 - (1) John T Aydelotte
 - (2) C H Beecher
 - (3) Robert U Patterson
- Bert Ernest Mulvey, Oklahoma City, Okla
 - (1) Wann Langston
 - (2) John E Heatley
 - (3) Lea A Riely

- Jesse Carl Painter, Dubuque, Iowa
 (1) John H Peck
 (2) C B Luginbuhl
 (3) Walter L Bierring
- Arthur Douglas Parker, Norfolk, Va
 (1) C L Harrell
 (2) Walter B Martin
 (3) J Morrison Hutcheson
- Herman Richard Parker, Greensboro, N C
 (1) Frederick R Taylor
 (2) P W Flagge
 (3) C H Cocke
- H Raymond Peters, Baltimore, Md
 (1) Louis Krause
 (2) Thomas P Sprunt
 (3) M C Pincoffs and Henry Thomas, Jr
- Joseph A Pollia, Los Angeles, Calif
 (1) John V Barrow
 (2) Samuel M Alter
 (3) Egerton Crispin
- Joseph W Post, Philadelphia, Pa
 (1) Frank W Burge
 (2) Edward L Bortz
 (3) Geo Morris Piersol
- Louis Elwood Prichman, Rochester, Minn
 (1) F W Gaarde
 (2) C K Maytum
 (3) E L Tuohy
- William Kendrick Purks, Vicksburg, Miss
 (1) W N Jenkins
 (2) Felix J Underwood
 (3) G W F Rembert
- John A Reisinger, Philadelphia, Pa
 (1) Alfred Stengel
 (2) O H Perry Pepper
 (3) Wm D Stroud
- Anthony J Rejent, Toledo, Ohio
 (1) C W Waggoner
 (2) L A Levison
 (3) A B Brower
- Russell Lowell Sands, Santa Monica, Calif
 (1) John V Barrow
 (2) Walter Wessels
 (3) Egerton Crispin
- Leon Schiff, Cincinnati, Ohio
 (1) H B Weiss
 (2) Henry Wald Bettmann
 (3) A B Brower
- Jesse Bedford Shelmire, Dallas, Texas
 (1) C Frank Brown
 (2) D W Carter, Jr
 (3) C T Stone
- Isaac Judah Silverman, Washington, D C
 (1) W A Bloedorn

- (2) C B Conklin
- (3) Wallace M Yater
- Stanley David Simon, Cincinnati, Ohio
 - (1) H B Weiss
 - (2) Henry Wald Bettmann
 - (3) A B Brower
- Edwin J Simons, Swanville, Minn
 - (1) J A Myers
 - (2) H A Burns
 - (3) S Marx White
- Francis Harper Sleeper, Worcester, Mass
 - (1) Helmuth Ulrich
 - (2) Herman C Petterson
 - (3) William B Breed
- Louis Sommer, Cincinnati, Ohio
 - (1) Henry Wald Bettmann
 - (2) H B Weiss
 - (3) A B Brower
- Will Cook Spain, New York, N Y
 - (1) Milton A Bridges
 - (2) J Russell Twiss
 - (3) Robert A Cooke
- Charles Henry Sprague, Des Moines, Iowa
 - (1) H A Collins
 - (2) Edward W Anderson
 - (3) Tom B Throckmorton
- Thomas Autin Starkey, Rochester, Minn
 - (1) George E Brown
 - (2) E V Allen
 - (3) E L Tuohy
- Gilbert Miller Stevenson, Pedro Miguel, C Z
 - (1) C D Briscoe
 - (2) Tomas Guardia
 - (3) Wm M James
- Charles Roberts Thomas, Chattanooga, Tenn
 - (1) Franklin B Bogart
 - (2) Wm D Anderson
 - (3) J O Manier
- Edwin T Thorsness, Casper, Wyo
 - (1) J C Kamp
 - (2) C F Morsman
 - (3) Adolph Sachs
- Pat Alexander Tuckwiller, Charleston, W Va
 - (1) Martin L Bonar
 - (2) R D Roller, Jr
 - (3) John N Simpson
- Leon Unger, Chicago, Ill
 - (1) A A Goldsmith
 - (2) Frederick Tice
 - (3) James G Carr
- Charles Edgar Virden, Kansas City, Mo
 - (1) Harry L Jones
 - (2) A Morris Ginsberg
 - (3) A C Griffith

Harry Walker, Richmond, Va

- (1) R Finley Gayle, Jr
- (2) Wm B Porter
- (3) J Morrison Hutcheson

Jacob Werne, Jamaica, L I, N Y

- (1) Morris Weisberg
- (2) Harlow Brooks
- (3) Luther F Warren and Robert A Cooke

Joseph H Whiteley, M C, U S A, Washington, D C

- (3) Robert U Patterson

Willard Ralph Wirth, New Orleans, La

- (1) I I Lemann
- (2) Randolph Lyons
- (3) J H Musser and J E Knighton

Burbridge Scott Yancey, Harrisonburg, Va

- (1) H B Mulholland
- (2) J Edwin Wood, Jr
- (3) J Morrison Hutcheson

ANNALS OF INTERNAL MEDICINE

VOLUME 8

FEBRUARY, 1935

NUMBER 8

THE SYSTOLIC MURMUR FURTHER OBSERVATIONS ON ITS CLINICAL SIGNIFICANCE *

By RICHARD D. FRIEDLANDER, M.D., *San Francisco, California*, and
MORTON G. BROWN, M.D., *Boston, Massachusetts*

THE clinical significance and the circulatory dynamic background of systolic murmurs have been subjects of considerable discussion for a great many years and probably will remain so ^{1,2,3,4}. The interpretations of such murmurs have varied from time to time. Once they were generally recognized as indicative of grave heart disease and later as having no meaning whatever. More recently a middle course has been taken by many of those interested in the subject ^{1,6}. The phenomenon is such that careful clinical observation in human beings offers the means of clarifying some of the confusion that exists. For this reason some simple observations on the production of the systolic murmur were made under control circumstances.

Transient systolic murmurs, which may be detected in a number of individuals with presumably normal hearts, can be divided into those which appear during the course of disease, such as hyperthyroidism, anemia, neuro-circulatory asthenia, fever, etc. and those which are artificially produced by exercise or the administration of certain drugs.

Several rather extensive studies have demonstrated how frequently systolic murmurs may occur during exercise. Munford ⁷ found that 7.8 per cent of 1552 students developed heart murmurs after exercise. MacKenzie ⁷ noted an incidence of 27.8 per cent in 266 apparently healthy students following exercise, while Siemsen ⁸ has reported the development of murmurs in 46 per cent of a group of 275 children and adolescents. Freeman and Levine ¹ were able to produce a systolic murmur of grade 1 or 2 intensity at the apex or base in 9 out of 10 normal persons after exercise and expressed the opinion that systolic murmurs appearing after effort, when not present previously, have no significance and may be found in most normal people.

Since amyl nitrite has been used for the purpose of accentuating or bring-

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From the Medical Clinic of the Peter Bent Brigham Hospital.

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ing out latent murmurs of organic origin,^{2, 8} it was felt that this drug, which is simple to administer, acts quickly and has no disagreeable after-effects, might be used in an effort to determine the incidence, location, and probable mechanism of transient systolic murmurs artificially produced. Similarly in an effort to study the transient murmurs, which appear during the course of an illness, a group of patients with fever were selected for observations, as well as a small group with various types of anemias.

One hundred patients on the medical and surgical wards of the Peter Bent Brigham Hospital known to have no heart disease were subjected to the inhalation of one perle of amyl nitrite (5 minims) until the full pharmacological effect was obtained. This was usually manifested in about 30 seconds by a feeling of fullness in the head, marked vasodilatation in the face and neck, a rise in heart rate and a fall in blood pressure. Auscultation of the heart, pulse readings and blood pressure determinations were recorded before, during, and after the action of the drug by two observers. All resultant murmurs were graded in intensity according to the classification described by Freeman and Levine,¹ who defined the faintest bruit definitely heard as grade 1, a slightly louder murmur as grade 2 and a murmur of moderate intensity as grade 3, up to grade 6, the loudest possible murmur.

Systolic murmurs were produced in 47 of the 100 cases. This is not in agreement with the findings of Kahler,² who claims that amyl nitrite seldom produces murmurs in normal hearts. These murmurs were produced in 4 per cent of the male patients and 44 per cent of the females. The extreme of ages for the entire group ranged between 12 and 57 years. There was, however, no striking difference in the average age of those in whom a murmur was produced and those in whom it was not. In the former the average age was 28.8 years as compared with 30.1 years in the latter group.

The average rise in pulse rate was approximately the same for those who developed murmurs and those who did not, being 54 beats per minute above the initial rate (table 1). This rise is about twice as great as that obtained by Cotton, Slade and Lewis.⁹ Similarly all patients, whether developing murmur or not, exhibited a substantial drop in the systolic and diastolic blood pressure of approximately the same magnitude. Following the subsidence of the amyl nitrite effect, there was usually noted in both groups a rise in blood pressure above the original resting level. In addition the observation was made in those patients developing a murmur, that the murmur frequently appeared as the pulse rate declined and the blood pressure rose above the initial level. From this it follows that the increase in rate is not the deciding factor.

The majority of the murmurs were heard at the base and in practically every instance both observers agreed as to their presence and intensity. In 38 instances a systolic murmur was audible over the pulmonic region, in 1 at the apex and in four over the aortic area (table 2). There were eight patients in whom murmurs were detected both at the pulmonary area and

TABLE I

| | Initial pulse rate | Pulse rate during amy nitrite effect | No of beats rise during amy nitrite effect | Initial blood pressure | | Blood pressure fall during amy nitrite effect | | Blood pressure rise after amy nitrite effect | |
|------------------------------|--------------------|---------------------------------------|---|------------------------|-----------|--|-----------|---|-----------|
| | | | | Systolic | Diastolic | Systolic | Diastolic | Systolic | Diastolic |
| Cases developing murmurs | 77.4 | 132.7 | 55.3 | 124.9 | 80.1 | 102.8 | 53.7 | 145 | 92.7 |
| Cases not developing murmurs | 82.9 | 136.6 | 53.7 | 124.1 | 75.2 | 101.0 | 53.6 | 150.8 | 97.5 |

apex, two over the pulmonary and aortic regions and one at the apex and aortic area (Table 3)

TABLE II
Location of Murmurs

| Intensity | Pulmonic | Apical | Aortic | Total |
|-----------|----------|--------|--------|-------|
| 1 minus | 2 | 1 | 0 | 3 |
| 1 | 9 | 4 | 4 | 17 |
| 1 plus | 14 | 8 | 0 | 22 |
| 2 | 7 | 1 | 0 | 8 |
| 2 plus | 6 | 2 | 0 | 8 |
| Total | 38 | 16 | 4 | 58 |

TABLE III
Location and Intensity of Combined Murmurs

| No. Patients | Pulmonic | Apical | Aortic |
|--------------|----------|--------|--------|
| 4 | 2 | 1 | - |
| 2 | 1 | 1+ | - |
| 1 | 1+ | 1+ | - |
| 1 | 1 | 1 | - |
| 1 | 2 | - | 1 |
| 1 | ? | - | 1 |
| 1 | 1 | - | 1 |

None of the murmurs was louder than 2 plus in intensity. In 16 individuals the intensity ranged from 2 to 2 plus, whereas in 31 the intensity ranged from 1 minus to 1 plus. In 27 patients the murmurs over the pulmonary orifice ranged from 1 plus to 2 plus and in 11 instances murmurs of the same range of intensity were present over the apical region. It is evident then, that not only was the greater number of murmurs heard over the pulmonary region, but that in this region they were of the greatest intensity.

Twenty-six observations were made in 20 patients with fever either artificially produced by intravenous typhoid vaccine or malaria during the course of treatment or as a result of illness. In only four were transient systolic murmurs produced during the height of fever. The average temperature of these patients was 104.4° F, while the average temperature of those in whom no murmurs appeared was 103.4° F. There were no substantial differences in the pulse rate or blood pressure readings in the patients who developed murmurs and those who did not.

Although there are other factors involved, it follows that fever alone can occasionally account for slight transient systolic murmurs.

The effect of anemia on the development of the systolic murmur was studied in a small group of cases. In three patients a systolic murmur was present during anemia, which disappeared when the blood returned to a higher level. The average hemoglobin in these three cases was 43 per cent and the average red blood cell count was 2.5 million. The corresponding determinations, when the murmur had disappeared, were 70 per cent and 4.1

million In one of these instances the murmur was of grade 2 plus intensity at the pulmonary and apical regions and in the other two the intensity was of grade 1 plus There were three cases in which no murmurs were heard during a moderate degree of anemia, when the average hemoglobin was 54 per cent and the red blood cell count was 2.3 million From this it seems that the relationship between anemia and a systolic murmur is inconstant There can be no doubt, however, that in some cases anemia, of itself, can account for the presence of a systolic murmur

A great many investigators believe that transient systolic murmurs are dependent upon the increase in blood velocity,^{1, 2, 4} inasmuch as the conditions in which they appear have been shown to have an increased velocity of blood flow¹⁰ Fahr⁴ has applied this principle in an interesting manner and an explanation may be made on the basis of the critical velocity of blood flow This factor has been defined as the velocity of flow in a vessel with parallel walls beyond which the flow is no longer steady and becomes turbulent Any considerable increase in velocity, therefore, determines turbulent flow Should the velocity of blood flow increase decidedly, one might expect the appearance of murmurs Since the greatest velocity is produced during systole, these murmurs should be largely systolic

Determinations of the rate of blood flow have been made in some of the conditions associated with a systolic murmur, such as hyperthyroidism and anemia, and found to be increased There are other states, however, notably neuro-circulatory asthenia, associated with a faint systolic murmur and a normal rate of blood flow Such hearts often have hypertonic sounds, as if the ejection of blood from the heart is snapping, as occurs in hyperthyroidism, and it is conceivable that the flow from the heart through the great vessels is increased in rate, although measuring the speed of blood through the entire circuit gives normal figures

It has been shown that nitrites increase the cardiac output¹¹ In addition animal experiments¹² have demonstrated that nitrites produce a rise in pulmonary arterial pressure as a result of greater minute output associated with cardiac acceleration and increased venous return, and that their effect upon pulmonary vessels is the same as on the systemic vessels, though less marked

Another group favors the relative changes between the heart and great vessels as the most probable causative factor^{2, 4, 13} In such circumstances a relative stenosis as represented by a more or less rigid pulmonary or aortic ring, associated with dilatation of the vessel beyond, would be conducive to the appearance of a systolic murmur at the base It has been shown that amyl nitrite produces a decrease in the size of the heart shadow in animals¹⁴ and in humans the drug has also produced a decrease in the transverse diameter of the heart and an increase in the aortic shadow, in which the pulmonary vessels probably play a part¹⁵ Since the walls of the pulmonary artery are generally more distensible than those of the aorta, a relative stenosis is likely to be more marked at the pulmonary orifice, thus resulting in systolic murmurs at this area more frequently The fact, that in this

series of cases given amyl nitrite the systolic murmurs were most frequently heard when the pulse rate had begun to drop and the blood pressure had risen above the initial level, seems to support the increased velocity of blood flow as a plausible explanation. It is possible that a relative stenosis may well be involved in this mechanism, also.

Furthermore, it should be mentioned that in the conditions investigated in this study no systolic murmurs of grade 3 intensity or greater were detected. This, we feel, is strong evidence in favor of the association of the louder murmurs with organic cardiovascular lesions.

CONCLUSIONS

1 Observations were made in 100 individuals, showing no evidence of heart disease, on the effect of amyl nitrite in the production of murmurs. In 47 individuals a systolic murmur developed. In none did a diastolic murmur or a systolic murmur of grade 3 intensity or greater occur. Murmurs of grade 1 intensity were about twice as common as grade 2 and they were more common at the pulmonary region than at the apex.

2 The systolic murmur that develops following amyl nitrite was found not to be due to the increased pulse rate but was found to be present as the rate began to slow.

3 Twenty-six observations in 20 patients were made on the effect of fever. In only four were systolic murmurs detected.

4 Observations in a small group of cases with anemia indicate that the relationship between anemia and the development of the systolic murmur is inconstant. There are some cases, however, in which the presence of the former, of itself, can account for the latter.

5 In the production of systolic murmurs a factor, that we regard as of some importance, is the velocity with which the blood is ejected from the heart. In many of the conditions (apart from organic heart disease) in which systolic murmurs are present, the velocity of blood flow is increased.

6 The fact that systolic murmurs of grade 3 or greater were not detected in the conditions that were investigated in this study, is further evidence that these louder murmurs are probably associated with organic cardiovascular disease.

The authors wish to express their appreciation to Dr. S. A. Levine for his many helpful suggestions and valuable criticism.

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THE DUAL NATURE OF THE ACTION OF INSULIN UPON THE HEART¹

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IN a previous communication¹ it was shown that the characteristic electrocardiographic changes resulting from insulin hypoglycemia could be obtained in elderly diabetic patients with cardiovascular disease, by the use of therapeutic doses of insulin in amounts which did not cause hypoglycemia. Since similar results could be obtained in these patients by the use of low carbohydrate diets without insulin, and since in both insulin hypoglycemia and in our therapeutic experiments the insulin effects tended to be reversed upon the administration of carbohydrate, it seemed probable that the electrocardiographic distortions were secondary to the effects of the insulin on the available carbohydrate supply rather than to a primary action of the insulin upon the myocardium. Our results, however, did not preclude the possibility that some of the deleterious effects of insulin might not be reversed by the administration of carbohydrate. This latter possibility led us to the present investigation on animals, in which a more rigorous separation of the two factors was possible.

Our first approach to the problem was to observe the effects of the administration of adequate doses of carbohydrate in animals which had received large doses of insulin. The carbohydrate was administered either before or after hypoglycemia had occurred. The results of these experiments made it desirable to study animals in which hypoglycemia was produced without hyperinsulinemia. For this purpose evisceration was employed.

METHODS

In the insulin experiments, our method was, in brief, to produce marked hyperinsulinemia at varying blood sugar levels. A dog was trained to lie quietly on his right side throughout the whole experiment. At the beginning of each experiment, electrodes, consisting of copper wire wound around flannel bandage soaked in concentrated salt solution, were applied to the shaven limbs. At appropriate times blood was obtained by venous puncture from the external saphenous vein and the blood sugar content determined by the Somogyi modification of the Shaffer-Hartman method.²

In the evisceration experiments hypoglycemia was obtained by removing the source from which the blood derives its sugar content.³ Complete evisceration was performed in preference to hepatectomy in order to remove the

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possibility of inadvertent hyperinsulinemia Complete eviscerations were performed both by the well-known two-stage method or by a modification of the newer one-stage method of hepatectomy described by Markowitz et al.⁴ The animals were fasted for 24 to 48 hours before evisceration Both the operations and the experiments were carried out under barbital anesthesia Electrocardiograms and blood sugar estimations were done as in the previous experiments, but since the animals were anesthetized it was found more convenient to use German silver electrodes inserted subcutaneously Blood samples were obtained from a cannulated artery In a few experiments blood lactic acid was also determined Mean arterial blood pressure was continuously recorded on a smoked drum from one carotid artery

Following the completion of the evisceration, simultaneous electrocardiograms and samples of blood for sugar analyses were taken at 20 minute intervals The first few blood sugar determinations were made as quickly as possible By plotting these values and projecting the curve, a rough estimate of the time at which the animal would enter an adequate hypoglycemic state could be made When, from this calculation, it was thought that the animal's blood sugar level had reached a point below 20 mg per cent, $\frac{1}{4}$ to $\frac{1}{2}$ gram dextrose per kg body weight was administered intravenously The animal was then observed during a second and sometimes a third such period

The possible effect of volume and fluid administration in the injection of dextrose was controlled in several experiments by the administration of equivalent amounts of isotonic saline

RESULTS

The electrocardiographic changes which we observed during insulin hypoglycemia were similar to those obtained by others and by ourselves in previous work (Cf figure 1) It may be seen that while glucose administration may completely reverse the insulin effects on the electrocardiogram (exp 2, table 1) this is by no means a constant result Furthermore, the degree of electrocardiographic distortion bears no constant relationship to the coincident blood sugar level (exps 3 and 4, table 1) These observations are also apparent in experiments 5 and 6 (table 1) where insulin was given with the glucose, after hypoglycemia had developed In experiment 7 (table 1) the electrocardiographic distortion occurred following the administration of insulin, in spite of the simultaneous and repeated administration of sufficient glucose to prevent hypoglycemia It is interesting to note that the electrocardiographic distortion in this experiment was greater at the higher blood sugar level than at the lower

These experiments indicate that insulin hypoglycemia is accompanied by electrocardiographic changes which may be only partially reversed by sugar administration and which bear no constant relationship to the blood sugar level The dual nature of this insulin effect led us to attempt to determine the effects of hypoglycemia not due to insulin

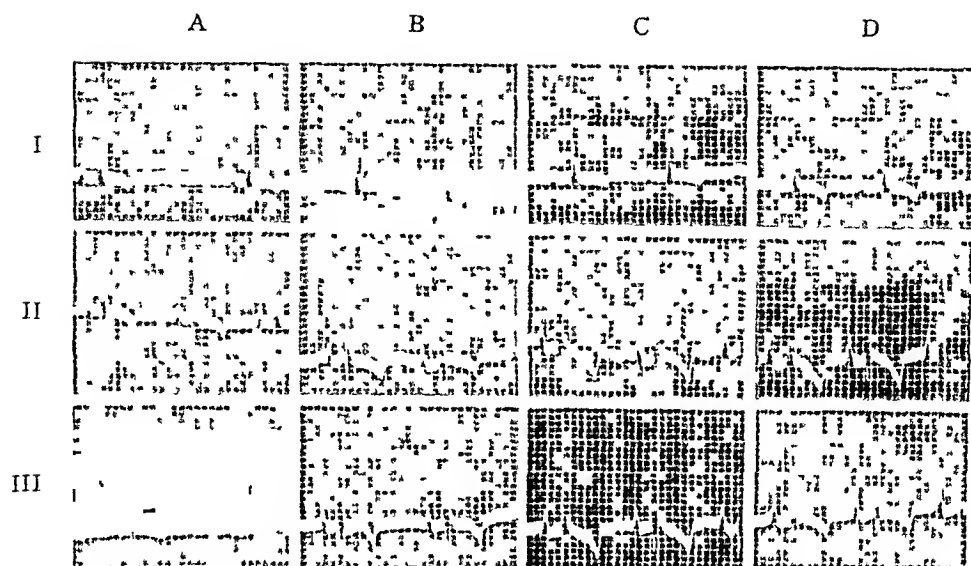


FIG 1 Electrocardiograms (experiment 4, table 1) showing the characteristic insulin effect on the T-wave. Segment A is the control, segments B and C show the progressive change. Segment D shows the persistence of this change following the elevation of the blood sugar by sugar administration.

In the evisceration experiments we observed changes in the electrocardiograms accompanying hypoglycemia, which were reversible upon the administration of dextrose.

Hypoglycemia caused a decrease in the amplitude of the upright T-wave, in all leads. (Our series contained no instance of an initially inverted T-wave.) In two cases the upright T-wave actually became inverted during hypoglycemia, in one instance this occurred in Lead I, in the other case (figure 2) it was seen in all leads. In one animal the control electrocardiographic records after operation showed inversion of the QRS complex in Leads II and III. Hypoglycemia in this case increased the amplitude of the upright T-wave in these leads*. In every case, the above changes persisted and progressed with the hypoglycemia, and the changes in the T-wave disappeared only upon the elevation of the blood sugar level by the administration of sugar. As illustrated in table 2, the magnitude of the changes due to hypoglycemia could not be strictly related to the degree of hypoglycemia which occurred. However, with two exceptions, no change was seen until the blood sugar fell below 30 mg per cent.

In addition to the hypoglycemia effects we also observed progressive changes in the electrocardiogram which bore no relationship to the glycemic level. These latter changes which were apparently related to the functional state of the circulatory system, progressed steadily, with the hypoglycemia effects superimposed upon them. Characteristic electrocardiographic

* This change in the T-wave is opposite in direction to that obtained in the other experiments, and is related to the reversed direction of the QRS complex. This confirms the conclusions drawn from similar observations in our previous work.¹

TABLE I
Insulin Experiments

| Exp No | Time | Material Administered | T-Wave Distortion * | Blood Sugar Level | Remarks |
|--------|------|-----------------------|---------------------|-------------------|---|
| 1 | Min | 15 units insulin † | 0 | Mg % 92 | "Control" experiment Insulin effect marked and progressive for 4 hours |
| | 0 | | | | |
| | 10 | | +++ | 17 | |
| | 130 | | +++++ | 15 | |
| | 190 | | +++++ | 11 | |
| | 250 | | +++++ | | |
| 2 | 0 | 16 units insulin | 0 | 80 | Insulin effect completely reversed by sugar |
| | 10 | | | | |
| | 110 | 13 gm glucose † | +++ | 22 | |
| | 120 | | 0 | 72 | |
| 3 | 0 | 17 units insulin | 0 | 84 | Insulin effect partially reversed by sugar, in spite of slight elevation in blood sugar level |
| | 10 | | | | |
| | 125 | 13 gm glucose | ++++ | 20 | |
| | 150 | | | | |
| | 190 | | ++ | 26 | |
| 4 | 0 | 15 units insulin | 0 | 87 | Insulin effect obtained at relatively high blood sugar level, and not reversed in spite of marked increase in blood sugar level |
| | 10 | | | | |
| | 70 | | ++ | 57 | |
| | 130 | 10 gm glucose | +++ | 42 | |
| | 145 | | | | |
| 5 | 0 | 15 units insulin | 0 | 87 | Insulin effect only partially reversed by large amount of sugar when insulin given with latter |
| | 10 | | | | |
| | 130 | 25 gm glucose | +++ | 13 | |
| | 155 | 15 units insulin | | | |
| | 210 | | ++ | 146 | |
| 6 | 0 | 16 units insulin | 0 | 72 | Insulin effect only partially reversed by large amount of sugar when insulin given with latter |
| | 10 | | | | |
| | 130 | 25 gm glucose | ++++ | 15 | |
| | 140 | 10 units insulin | | | |
| 7 | 0 | 20 gm glucose | 0 | 80 | Insulin effect not prevented by simultaneous and continued sugar administration |
| | 10 | 15 units insulin | | | |
| | 70 | 8 gm glucose | | | |
| | 115 | | ++ | 94 | |
| | 130 | 8 gm glucose | + | 40 | |
| | 230 | | | | |

* The electrocardiographic T-wave changes are recorded in arbitrary units to indicate in a semi-quantitative manner the relative amount of change observed by comparing the entire series of records. Figure 1 depicts typical electrocardiographic changes of degrees ++ and +++ 0 indicates the control contour

† Insulin given subcutaneously, glucose intravenously

TABLE II
Evisceration Experiments *

| Exp No | Blood Sugar Level | Blood Pressure | T-Wave Distortion |
|--------|-------------------|----------------|-------------------|
| | mg % | mm Hg | |
| 1 | 215 | 90 | 0 |
| | 59 | 65 | 0 |
| | 413 | 65 | 0 |
| | | | |
| 2 | 242 | 62 | 0 |
| | 125 | 63 | 0 |
| | 350 | 63 | 0 |
| 3 | 87 | 77 | 0 |
| | trunc | 58 | + |
| | 65 | 55 | 0 |
| | 4 | 55 | + |
| | 108 | 58 | 0 |
| 4 † | 53 | 160 | 0 |
| | 15 | 38 | ++ |
| | 92 | 75 | 0 |
| 5 | 98 | 85 | 0 |
| | 11 | 70 | + |
| | 83 | 85 | 0 |
| | 9 | 70 | + |
| | | | |
| 6 ‡ | 49 | 170 | 0 |
| | 26 | 167 | ++ |
| | 9 | 115 | ++++ |
| | 157 | 120 | 0 |
| | 13 | 60 | + |
| | 237 | 80 | 0 |
| | | | |
| 7 | 115 | 180 | 0 |
| | 74 | 125 | 0 |
| | 173 | 120 | 0 |
| | 94 | 115 | + |
| | 222 | 90 | 0 |
| 8 | 75 | 135 | 0 |
| | 28 | 50 | + |
| | 109 | 45 | 0 |
| | 22 | 50 | + |
| 9 § | 52 | 125 | 0 |
| | 15 | 80 | ++ |
| | 153 | 100 | 0 |
| | 11 | 75 | + |
| | 248 | 78 | 0 |
| 10 | 77 | 120 | 0 |
| | 22 | 23 | +++ |
| | 178 | 20 | 0 |
| | 37 | 18 | + |
| 11 | 45 | 150 | 0 |
| | 8 | 125 | + |
| | 53 | 140 | 0 |
| | 19 | 135 | + |
| | 177 | 115 | 0 |

* Summary table of approximately the highest and lowest points of the experiments as regards the blood sugar level. The values in each experiment are given in chronological sequence. Rough quantitation of the T-wave changes as in table 1. Figure 2 depicts typical T-wave changes of degrees ++ and ++++. 0 indicates the control contour.

† QRS diphasic in Lead II, inverted in Lead III.

‡ Direction of T-wave reversed.

§ QRS inverted in Leads II and III.

|| Direction of T wave reversed in Lead I.

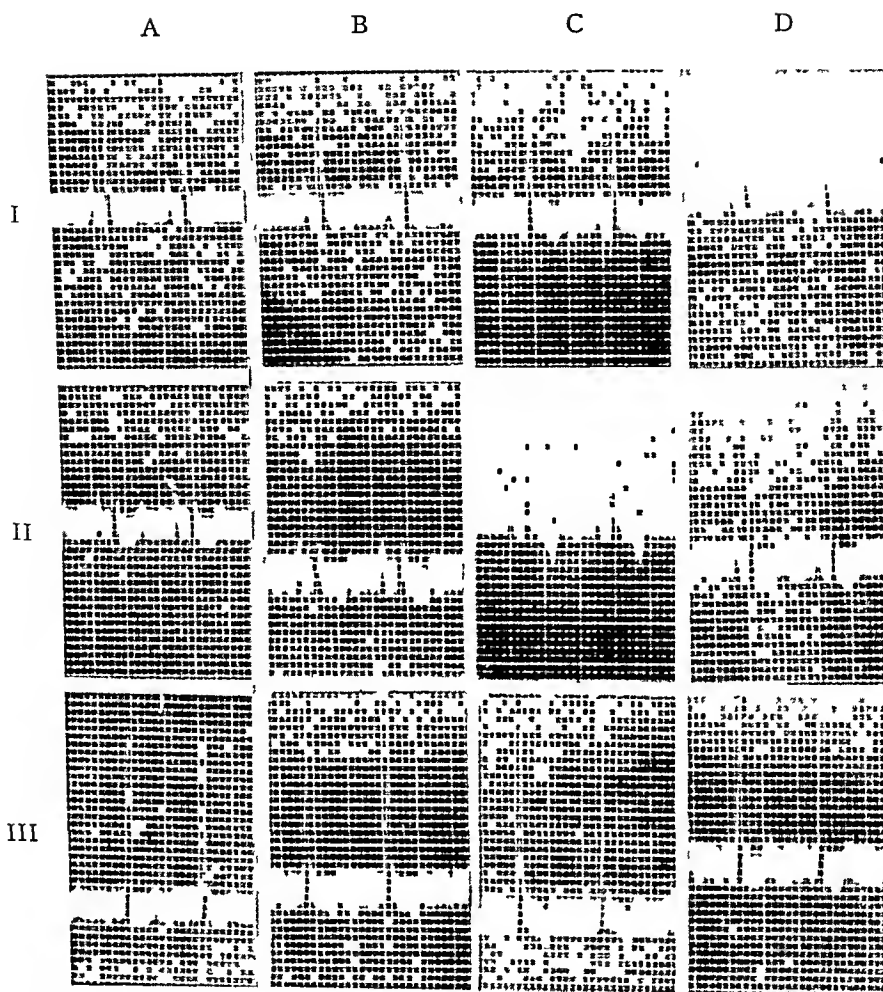


FIG 2 Electrocardiograms (experiment 6, table 2) showing reversal in direction of the T-wave in all three leads during hypoglycemia produced by evisceration. Segments A, B and C are records taken at increasing intervals after the evisceration, at blood sugar levels of 49, 26, and 9 mg per cent respectively. Segment D is a record taken after the administration of dextrose, when the blood sugar level was 157 mg per cent. This shows the completely reversible nature of the T-wave change caused by hypoglycemia without hyperinsulinemia.

changes, unrelated to the glycemic level, also appeared when the blood pressure fell to extremely low levels. In such instances, an increase in blood pressure brought about by the injection of isotonic saline, returned the electrocardiogram toward normal. However, saline repeatedly failed to affect the electrocardiographic changes accompanying hypoglycemia, which were reversed by the injection of sugar.

These results demonstrate beyond doubt that hypoglycemia per se affects the electrocardiogram.*

* At the suggestion of Dr A. B. Luckhardt we attempted to observe the effects upon the electrocardiogram of chronic hypoglycemia caused by continued phlorhizin administration. We found, however, that phlorhizin produces electrocardiographic changes which differ from those produced by insulin and which, furthermore, are not reversible by raising the glycemic level.

SUMMARY AND CONCLUSION

1 Insulin hypoglycemia is accompanied by electrocardiographic changes which are only partially reversible by the administration of sugar. In addition to its hypoglycemic effects, insulin has been shown to affect the electrocardiogram through some other mechanism.

2 It has been shown that hypoglycemia without hyperinsulinemia produces electrocardiographic variations which are completely reversible by the administration of sugar.

3 Our present results indicate that some of the electrocardiographic changes obtained in our previous studies upon elderly diabetic patients with cardiovascular disease,¹ must have been due to that action of insulin which is not reversed by carbohydrate. In the light of our previous work it may therefore be concluded that the deleterious action of insulin on the heart, associated with the electrocardiographic changes, probably cannot be completely antidoted by adjusting the carbohydrate intake. This does not vitiate our previous conclusions as to the importance of an adequate carbohydrate supply to counteract the harmful effects of relative or absolute hypoglycemia. It does, however, direct attention to the necessity for further study of the significance and extent of the possible harm which may result from that action of insulin which is not related to the hypoglycemia.

We are indebted to the Department of Chemistry for assistance with chemical determinations.

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A CRITICAL REVIEW AND EVALUATION OF TESTS FOR LIVER FUNCTION [†]

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THE functions of the liver have been shown by Mann¹ and his co-workers to vary more or less independently of one another, and disturbances or cessation of one function may be coincident with normality in the other. Therefore, it is necessary to have an understanding of the various functions of the liver before a clear conception of the different tests for liver function can be discussed.

In order fully to understand the various functions of the liver certain anatomical, physiological and chemical aspects of this organ must be considered.

It is a well known fact² that the liver has great power of regeneration, and even in a case where liver damage clinically seems very evident, enough regenerated tissue may have formed to make functional tests appear as though the liver were normal. A large amount of structural change may be present in the liver before a functional disorder is evident, and on the contrary a very marked derangement of function may be present without any structural change in the liver. However, when symptoms of liver diseases are very marked there is usually some structural change that can be observed.

The liver is thought to be more or less concerned with the following functions:

- 1 The secretion and excretion of bile
- 2 The destruction of red blood cells
- 3 The coagulation of the blood
- 4 The storing of fat taken from the food to be set free as required
- 5 The metabolism of proteins and the formation of urea
- 6 The formation of glycogen from ingested carbohydrates and proteins, reconversion of glycogen into glucose as required for the nutrition of the body
- 7 The protective function of detoxicating poisons brought to it from the gastrointestinal tract and other parts of the body, and the removal of foreign substances from the blood
- 8 The rôle played in concentration and dilution of the blood plasma in heat regulation

It is not within our province to enter into a discussion of all the physiological facts concerned with these functions, and we refer to recent text-

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books and articles on the advance in physiology in the past few years for details

Over a period of years, methods have been devised to test most of these separate functions of the liver, but none has been advanced that will evaluate these functions as a whole, so it is necessary to study each function separately

In certain instances most of these functions have been tested at about the same time to determine the relationship of each, in the hope that some composite test may be devised to give us a better understanding of liver function as a whole

Since we³ started the study of liver function in 1925, an attempt has been made to gather some data on patients studied with all the known tests. So far no definite conclusions can be drawn, but it is hoped to publish definite data in the near future which may throw some light on this rather indefinite subject

Some tests act as a test for several functions, and it is hard to classify each under its separate function. Many writers⁴ in the past few years have given a very clear conception of the various tests in their reviews, by grouping the tests under functional heads

THE SECRETION AND EXCRETION OF THE BILE

It is possible to study the activity of the secretion of the bile by (1) a study of hepatic products in the stool and urine, (2) a study of the duodenal contents by drainage, and (3) a study of the rate of disappearance from the blood stream of substances specifically secreted by the liver

Inasmuch as disease of the gall-bladder is often associated with chronic inflammation of the liver and of the biliary passages, one must consider this organ as a factor in the picture of liver disease and determine if it is involved in the process. However, in most cases of cholecystitis the changes produced have very little effect on the functional efficiency of the liver

Although not considered as strictly a test for liver function, the method of cholecystography as introduced by Graham and Cole in 1924, has been of great help in differentiating gall-bladder from liver disease

The intravenous injection of thorium dioxide, followed by roentgen-ray pictures of the liver, has been used by Yater and Otell,⁵ to demonstrate cancer, cirrhosis, cysts and abscesses of the liver. Very definite pictures, useful in differential diagnosis, of these conditions can be obtained by this method

Likewise, the study of the duodenal contents by Lyon's⁶ drainage method, as suggested by Meltzer,⁷ is very helpful in the study of infections of the gall-bladder, biliary tract and liver, as well as to determine if jaundice is caused by obstruction of the common bile duct or due to other causes. The microscopic study of bile obtained by duodenal drainage is important, as it may reveal evidence of definite infection, or of crystals of cholesterol or calcium bilirubinate, which are important in the diagnosis of cholelithic disease

All are familiar with the value of the well known tests for bile pigment in the urine, with the associated absence of bile pigments in the stools, in determining obstructions of the biliary flow

The view of Aschoff⁸ that bilirubin is developed in the reticulo-endothelial system, from the destruction of red blood cells, is supported by McNee⁹ and others. Cells of this system are found in the spleen, bone marrow, lymph glands and interstitial cells of the testis, and the Kupffer cells of the liver. The bilirubin thus formed is passed through the polygonal cells of the bile capillaries, and after passing into the bile passages is oxidized into biliverdin. The bile pigment thus passes into the intestinal tract and, as shown by Wallace and Diamond¹⁰ and others, is converted into urobilin and urobilinogen. That part of the urobilin which is not excreted with the feces as stercobilin, is reabsorbed into the portal circulation and carried back to the liver where it is reconverted into bilirubin.

From this it can be readily seen that if there is parenchymal liver damage, the urobilinogen will not be taken up by the liver, but will be shunted into the general circulation. Due to the fact that the kidney threshold for urobilinogen is very low, it is rapidly excreted in the urine. When complete obstruction of the biliary flow is present, no bilirubin as biliverdin can enter the intestinal tract, and consequently no urobilin can be formed. In non-obstructive diseases of the liver in which there is parenchymal damage, the bilirubin finds its way into the blood stream by the liver cells and appears in the urine in increased amounts.

From the foregoing, the importance of an estimation of the bilirubin, urobilin and urobilinogen in the urine, as well as of bilirubin in the serum becomes evident.

Icterus Index The amount of bilirubin in the plasma is determined by the icterus index. The simplest method is that described by Mullengracht and modified by Maue.

"Approximately 5 c.c. of blood is withdrawn from a vein into a clean, dry test tube. The serum is carefully pipetted off, and a comparison of color is made in a colorimeter, against a standard 1 to 10,000 solution of potassium bichromate. The standard is set at 15 mm and this number divided by the number on the serum scale, represents the icterus index. If the serum is highly colored, suitable dilutions must be made before reading. The icterus index for normal sera falls between 4 and 6, and in most cases ranges around 5. The point at which visible jaundice appears varies considerably in different cases, but generally is around 15."

"There exists then, a zone of bilirubin retention that can be detected by this test, though no visible jaundice is present." The progress of the jaundice either upwards or downwards may be followed by this method.

However, in chronic liver disease, the icterus index is of little value, except to follow the course of the disease and to detect the early onset of jaundice.

The Van den Bergh Test By means of the Van den Bergh test it is

possible to determine if the bilirubin present in the blood serum has passed through the polygonal cells into the bile and been shunted back into the blood stream, because of obstruction to the bile passages. Under these circumstances the test yields the so-called "direct reaction." If the bilirubin present is due to the breakdown of hemoglobin, and has not passed through the polygonal cells of the liver, and possibly only through the Kupffer cells, the reaction is "indirect."

To perform this test, a solution "A" is made from 1 c c of sulphanilic acid, 15 c c concentrated HCl and 1000 c c of distilled water. Solution "B" consists of 0.5 gram of sodium nitrite and 100 c c of distilled water. Immediately before use, 25 c c of solution "A" and 0.75 c c of solution "B" are mixed.

The blood is allowed to clot and the serum used.

Direct Reaction One c c of serum and 1 c c of the mixed reagent are mixed. A bluish-violet color, which develops in from 10 to 30 seconds, is called a direct reaction. A small flake of caffeine sodium salicylate will hasten the reaction.

Indirect Reaction To 1 c c of serum 2 c c of 96 per cent alcohol are added, centrifuged, and 1 c c of the fluid is pipetted off.

To this is added 0.5 c c of the mixed reagent. If a violet-red color develops at once, an indirect reaction is present.

To be decisive, the color change in the direct reaction must come on in from 10 to 30 seconds. A delayed direct reaction appearing in from 1 to 15 minutes has the same significance as an indirect reaction. Biliverdin is formed only in the bile passages as the result of oxidation of bilirubin, and is not present in the blood stream and does not give a Van den Bergh reaction.

Both reactions may be present in the same case, giving a so-called "biphasic reaction," which is usually found in toxic or infectious jaundice. This may be accounted for by the fact that the bilirubin in the blood, due to obstruction of the bile ducts, gives a prompt direct reaction, while the bilirubin dammed up from poisoning of the liver, gives a delayed direct reaction. Also, in hemolytic jaundice the increased viscosity of the bile may result in blockage of the bile capillaries, and both forms of bilirubin will be present in the blood, giving rise to a biphasic reaction.

The amount of bilirubin in the blood serum may be quantitatively estimated. As Van den Bergh says, this is not a quantitative determination, but "an estimation," by using the indirect reaction as mentioned above. McNee¹¹ suggests the addition of 1 c c of saturated ammonium sulphate to the mixture, centrifugation and comparison with a standard solution made of cobaltous sulphate. The normal amount of bilirubin present in the blood serum by this method is from 0.2 to 1.0 mg per 100 c c (0.4 to 2 units). Recent findings of Jacobi¹² et al indicate that the plasma instead of the serum may be used with equal accuracy in determinations of bilirubin.

Trumper and Cantarow¹³ state that in selected cases of slight liver damage, it is possible to recognize liver insufficiency by the method of Harrop and Barron, in which bilirubin is injected intravenously, 1 mg per kilogram of body weight. In normal persons it should be excreted from the blood stream in two to four hours. If bilirubin is still present at the end of four hours, the power of the liver to excrete the pigment is impaired.

THE DESTRUCTION OF RED BLOOD CELLS

As has already been shown, this function of the liver is shared by other organs of the body, through the reticulo-endothelial system. A test of this function is not one of true liver function, but rather of hemolytic jaundice. However, the indirect Van den Bergh reaction, as already mentioned, is really a test of this function.

Greene, Snell and Walters¹⁴ state that "in uncomplicated cases of hemolytic jaundice, the pertinent laboratory data are anemia and microcytosis, the high reticulocyte count and the increased fragility of the erythrocytes. The concentration of serum bilirubin, and the icterus index, are increased to a moderate degree, the former rarely exceeding 10 mg in each 100 cc. The Van den Bergh reaction is persistently indirect. This association of clinical jaundice with an indirect Van den Bergh reaction is diagnostic of a hematogenous type of jaundice. The coagulation of the blood is not disturbed. There is no retention of bromsulphalein or phenoltetrachlorophthalein. Duodenal drainage usually discloses a free flow of bile, with an increased content of bilirubin. The urine contains large amounts of urobilin and urobilinogen, and bilirubin is absent."

THE COAGULATION OF THE BLOOD

It has been observed¹⁵ both clinically and experimentally that the coagulation time may be increased in diseases of the liver.

Although we have for some years given calcium by mouth and vein in jaundiced cases, to prevent bleeding, even if the serum calcium was normal, in the hope that an excess would help in the process of coagulation, recent studies seem to show this procedure is of no avail. Gunther and Greenberg¹⁶ have shown that there is no deficiency in diffusible calcium of the blood serum in jaundiced cases, and it is this diffusible calcium that is available for clotting. They conclude that factors other than calcium must be sought in order to explain the abnormal bleeding of jaundiced patients.

This further supports the theory, as advanced by Howell¹⁷ and others, that the liver is the principal site of the formation of fibrinogen.

If the liver is damaged to any extent, the blood fibrinogen is decreased, clotting time of the blood is increased and hemorrhage is apt to occur. As liver damage is repaired, the normal characteristics of the blood are restored.

It can readily be seen that the determination of the coagulation time is a very important test of this function of the liver. The sedimentation test¹⁸

is very useful⁷ in conjunction with the coagulation test, in order to detect a hemorrhagic tendency in patients. If the sedimentation rate is slow, hemorrhage is not so apt to occur, but if in the absence of fever, the rate is high, hemorrhage is more apt to occur.

FAT METABOLISM

Fats are brought to the liver for storage to be acted upon before they are utilized. It is generally believed, but not proved, that H_3PO_4 and nitrogenous bases are added to the fatty acids in the liver to form phospholipines, which are sent to the tissues.

Enzymes, which possess the power of hydrolizing fats, are widely distributed in the body and are known as lipases. Whipple¹⁰ has shown that injury to the liver causes a rise of blood lipase and has devised a test to measure this abnormality.

Normally, in terms of tenth normal acid, the blood lipase should be from 20 to 30 c c in normal persons and is usually constant. In liver necrosis Whipple has shown the blood lipase rises from five to eight times the normal level. He found a distinct rise when liver necrosis is produced by eclampsia, toxic poisons, acute yellow atrophy, cholangitis and abscess of the liver. Cirrhosis of the liver usually shows a subnormal blood lipase. True eclampsia may be differentiated from the toxemias of pregnancy by this test, as the toxemias usually do not produce a marked liver damage.

The method used by Whipple²⁰ is as follows: "Four tubes are prepared, each containing 1 c c of plasma or serum diluted with 4 c c of distilled water and 0.3 c c of toluol to check bacterial activity. To two tubes is added 0.26 c c of ethyl butyrate, the other two tubes serving as controls. The tubes are shaken, corked and placed in an incubator at 38° C for 18 to 24 hours. They are then cooled in ice water, three drops of azolitmin added and titrated in pairs to a neutral reaction, using 1/10 normal acid and alkali." The two control tubes usually show the blood alkalinity to be 0.10 c c of 1/10 normal acid. The butyrate tubes give the amount of acid production beyond the neutral point, and represent the total acid production or lipolytic activity. In normal blood it is usually from 0.20 to 0.30 c c and may be called the amount of lipase in the blood serum or plasma as the case may be.

Rowntree, Marshall and Chesney²¹ have made a comprehensive study of blood lipase in a variety of liver conditions and do not find it of much help in the diagnosis of early hepatic disease. K. C. Paul²² reviews many papers on this subject, but does not express his own opinion of this method. Personally we have not had enough experience with estimations of blood lipase to give an opinion as to its value.

Under the function of fat metabolism we must not forget that satisfactory fat absorption is dependent on an adequate supply of bile salts in the small intestine. Consequently, excessive amounts of fat, soap fat and free

fatty acid will be found in the feces in any condition causing obstruction of the bile passage and causing obstructive jaundice

PROTEIN METABOLISM

The liver plays a very important part in normal protein metabolism. Urea is formed in the liver after the deamination of amino-acids. Investigation of liver function, from the standpoint of protein metabolism, is chiefly concerned with the excess of ammonia or decrease of urea in the urine, also with the ratio of blood urea nitrogen to the total urinary nitrogen. Mann has shown, however, that 90 per cent of the liver must be damaged before this function is impaired. Due to the fact that these tests show changes only in far advanced hepatic disease, they are of serious prognostic significance, but of no value as early diagnostic aids.

Hemoclastic Crisis Test If there is enough damage to the liver to cause the entrance of protein split products into the circulation, an anaphylactic reaction is produced which is evidenced by a leukopenia and other anaphylactic phenomena. Based on these facts, the hemoclastic crisis test of Widal has been advocated as a method of study of liver function.

This test consists of giving a patient, on a fasting stomach, 200 c c of milk and taking a white count before ingestion of the milk, and repeating the count afterwards at 20 minute intervals for an hour, or until the leukocytic count has reached its minimum value. According to Snyder,²³ the blood pressure may show a slight change or may decrease 10 to 20 millimeters, the coagulability of the blood increases, the refractive index of its serum decreases markedly, and at the end of 90 minutes these changes proceed in the opposite direction.

This test, as shown by Fetter²⁴ and many others, has very little value in the diagnosis of liver disease since other factors, besides liver damage, can cause a variation in the leukocyte count and in the other phenomena. We have come to the same conclusion after using it for a very short time.

Uric Acid Mann² and his co-workers in their experiments on dogs have used the level of uric acid in the blood and urine as a hepatic function test. They show a very definite increase in uric acid in both blood and urine after removal of hepatic tissue. Mann thinks this is the most efficient of the liver function tests performed on dogs. This test has not been proved of value in humans, due to the fact that large injections of uric acid may cause lesions in the kidney.

Minot and Cutler¹³ have shown that the guanidine of the blood is increased in patients with acute arsphenamine hepatitis, acute catarrhal jaundice, preeclamptic toxemia and eclampsia, but that there is no deviation from the normal blood guanidine in chronic liver diseases such as carcinoma, syphilitic hepatitis, alcoholic cirrhosis and obstructive jaundice.

CARBOHYDRATE METABOLISM

As is well known, the liver plays a very important role in carbohydrate metabolism. As early as 1874 Bock and Hoffman²⁵ found that the blood

sugar was diminished after the liver had been cut off from the circulation. In 1901 Strauss²⁶ first suggested the use of levulose for testing liver function. He found that about 80 per cent of patients with liver disease exhibit a diminished tolerance for levulose, as evidenced by appearance of this substance in the urine. However, 10 per cent of normal individuals react positively to the levulose test.

In 1906 Bauer²⁷ first suggested the use of galactose as a better test for this function. The repeated experiments and classic investigations of Mann and his co-workers²⁸ have done a great deal to establish the importance of this test for liver function. Shay²⁹ and his co-workers have formed the conclusion that galactose offers the best means of investigating the carbohydrate function of the liver. They do not consider it an adequate routine test for liver function, but because of its limitations think it is ideal as an aid in the differential diagnosis of jaundice, and offers a means of identifying early the group of toxic or infectious jaundice.

Galactose Tolerance Test The test is as follows:

The patient is fasted for 12 hours, the patient voids and the specimen is examined for sugar. Forty grams of pure galactose are given by mouth to the patient, dissolved in 500 c.c. of water which may be flavored with lemon juice.

Urine is collected if possible every hour for five hours. Each specimen is examined qualitatively for sugar by Benedict's test, and the total amount voided is then tested quantitatively for sugar and the total amount of galactose secreted in the urine is calculated. As much water as desired is given during the test, but nothing else.

In diabetic persons the dextrose may be removed from the urine by fermentation with yeast, leaving only galactose. In normal persons with no disturbances of the carbohydrate function of the liver, about 3 grams of galactose may be excreted in five hours, any amount over this may indicate hepatic impairment. Jaundice accompanying acute diffuse damage of liver cells will give a high value. The carbohydrate function of the liver is impaired and allows the galactose to pass into the general circulation whence, due to the absence of a kidney threshold for galactose, it passes into the urine. In obstructive jaundice without liver damage and in hemolytic jaundice the readings are normal.

THE ANTITOXIC AND PROTECTIVE FUNCTION OF THE LIVER

The liver is known to possess a detoxifying function in protecting the body against various toxic substances, entering through the intestinal tract. Such substances as indol, salicylic acid, cinchophen, menthol, camphor, phenol, etc., are believed to be oxidized in the liver or conjugated into relatively nontoxic substances and eliminated in the bile and urine. Various methods, based on these facts, have been proposed for the estimation of liver function, but until of late none has proved to be of any clinical value.

Recently Lichtman³⁰ has reported a test based on the oxidation of cinchophen for estimating the function of hepatic cells and reports enough data on cases tested by his method to entitle it to serious consideration

This test is based on the fact that after the ingestion of cinchophen a product of oxidation oxy-cinchophen [2-(ortho-hydroxy)-phenyl-quinoline-4 carboxylic acid] appears in the urine. In disease conditions of the liver a larger percentage of oxy-cinchophen is excreted in the urine than is found in normal subjects. This is probably due to the fact that oxy-cinchophen represents an intermediary product in the destruction of cinchophen. The power of further catabolism of oxy-cinchophen is lost by damaged liver cells, and as the disturbance of the function of the cells increases, larger amounts of the oxy-cinchophen are excreted in the urine.

Cinchophen Test The test is performed by giving the patient 0.45 gram of cinchophen and then estimating for 24 hours the amount of oxy-cinchophen in accurately measured specimens of urine at two hour intervals during the day and in a night specimen. This is done by boiling 5 to 10 c.c. of each specimen and filtering, and then to 0.2 c.c. of each filtrate adding concentrated hydrochloric acid to make a volume of 5 c.c. The mixture is shaken and brought to a boil. When bile is present only 0.1 c.c. of urine may be sufficient. If a yellow color does not appear, 0.4, 0.6 or 0.8 c.c. respectively of urine is added to concentrated hydrochloric acid to make a final volume of 5 c.c. and similarly treated until such a reaction has taken place. These tubes are then compared with a set of standard tubes containing oxy-cinchophen. "The percentage of oxy-cinchophen determined colorimetrically represents the concentration of this substance in 0.1, 0.2, 0.4, 0.6 and 0.8 c.c. of urine, respectively, diluted to a final volume of 5 c.c. It must be multiplied by the respective dilutions, 50, 25, 12.5, 8.33 or 6.25 to obtain the percentage of oxy-cinchophen in the original urine." The total amount of oxy-cinchophen is then calculated for the entire urine voided for 24 hours.

Lichtman believes this test measures quantitatively the extent of damage or dysfunction of the cells of the liver, and depends on a metabolic function of the liver that is apparently first to be disturbed in hepatic disease.

From our limited number of cases tested by this method, we have been unable to form any definite conclusion. In far advanced liver disease the results are not very satisfactory, but as a whole, we believe it offers many possibilities for future study.

THE REMOVAL OF FOREIGN SUBSTANCE FROM THE BLOOD

For many years it has been known that dyes are removed from the circulation and eliminated almost entirely by the liver. Various dyes as asorubin S, rose bengal, phenoltetraiodophthalein, phenoltetrachlorophthalein and bromsulphalein have been used as a basis for liver function tests.

Bromsulphalein Test In our own studies³ with dye as a liver function test, we have used bromsulphalein and the technic, with slight changes, as introduced by Rosenthal and White³¹ almost exclusively

The technic briefly is as follows. A 5 per cent solution of bromsulphalein on a basis of 2 mg per kilo of body weight is injected intravenously. At the end of 30 minutes blood is withdrawn from a vein on the opposite arm. After the blood has coagulated and is centrifuged the serum is removed, placed in two small tubes and four drops of 5 per cent sodium hydroxide are added to one tube to bring out the color of the dye, and four drops of 2 per cent hydrochloric acid added to the other to clear the serum. The amount of dye present is estimated by direct comparison with a series of standards by placing the cleared serum in front of a standard tube and comparing with the colored alkalinized serum.

In our³ original work by estimating the dye present in the serum 5, 15 and 30 minutes after injection of the dye we established a standard of 28, 15 and zero respectively. For this, 25 cases were used in which the liver was proved to be normal at operation or autopsy, and all cases not so proved were not used.

From the series of pathological cases studied, we concluded that in all cases of liver destruction, the percentage of dye retention increased with advance of the disease, while in the extra-hepatic diseases with obstruction, the retention was high when obstruction was present, and decreased with removal of the obstruction. Also, that in the more destructive diseases as cancer, cirrhosis, etc., the retention of the dye at the end of five and 15 minutes was somewhat higher than in cases of liver enlargement from obstruction of the mechanical or catarrhal type.

Since our original observations, we have used a dosage of 5 mg of dye per kilogram of body weight in cases where very slight liver damage was evident. Dye retention has been thus demonstrated in cases of slight liver damage which would be negative with the earlier technic. Nevertheless, even by this method we have found some cases with definite liver destruction at autopsy or operation, that showed no dye retention.

We still believe and agree with Robertson, Swalm and Konzelmann,³² who in their recent article state that dye retention will detect impairment of liver function as frequently as any other test, and that this test along with an icterus index determination, most frequently agrees with the clinical picture present.

Rosenthal,³³ who originally introduced bromsulphalein as a liver function test, still thinks that in chronic liver disease the dye test will be positive more often than the serum bilirubin, but that some cases of latent jaundice occur in which an increase of serum bilirubin is present without dye retention, so that both tests should be employed. He also states that experimental and clinical experience has shown that in no case, in the absence of liver disease, is there retention of dye, and that definite retention is almost certain evidence of liver damage.

Rose Bengal Test Our experience with the rose bengal dye test is very limited. Delprat and Stowe³⁴ think it is the best of the dye liver function tests and easiest performed. Kerr⁴ favors this test over bromsulphalein, as rose bengal is eliminated entirely through the liver while the former is partly excreted by the kidneys.

The test is performed by injecting 10 c.c. of a 10 per cent solution of rose bengal intravenously, and taking samples of blood after a period of two and eight minutes. Colorimeter comparisons are then made with the two minute specimen as a standard and the amount of dye estimated. In a normal functioning liver this test should show about 50 per cent less dye in the eight minute specimen than is found in the two minute specimen. Failure to remove this amount of dye is a sign of diminished liver function.

THE ANHYDROUS FUNCTION OF THE LIVER

It has been shown by Barbour³⁵ and Marshall that when the body temperature is raised by fever, a large amount of fluid is lost from the blood stream and stored in the liver. It is thought that this may be due to chemical changes in the liver. Some clues to this problem are found in the work of Hashimoto and Pick³⁶ which showed an increase of nonprotein nitrogen in the liver, following anaphylaxis. Barbour and Marshall think glycolysis may be a factor. A water balance test has been suggested by foreign writers³⁷ to test this function of the liver. So far it has not been developed enough in this country to be of any proved clinical value.

SUMMARY

While an attempt has been made briefly to give the physiological principles underlying the various tests for liver function, there appears to be no experimental proof of a physiological basis for some of them. However, most of the tests are of clinical value, inasmuch as they are an index of disease present in the liver, as proved clinically or by inspection of the liver at operation or autopsy.

In order to arrive at any definite conclusion, it is necessary to perform as many of the functional tests, herein described, as can be conveniently done. In certain chronic diseases of the liver, in which the remarkable ability of the liver to regenerate has a chance to exert itself, most of these tests will show no impairment. If each case is carefully studied by the above mentioned tests, a very good clinical picture of the liver for practical purposes is presented.

It is impossible to state which tests should be used in all cases of liver disease. In most cases it is necessary to perform the bromsulphalein test, the icterus index test, the Van den Bergh test, the galactose tolerance test, to determine the amount of bilirubin and urobilin in the urine, and to study the cells of the blood before any definite diagnosis of liver disease can be attempted. If further data are necessary, many of the other tests may serve as aids in diagnosis.

CONCLUSIONS

- 1 No liver function test has yet been developed to measure the functions of the liver as a whole
- 2 The various tests of different functions must be performed in order to give an understanding as to the liver damage as a whole
- 3 The regenerative power of the liver may cause a discrepancy in the results obtained by the various tests
- 4 Recent experiments and studies have made liver function tests more accurate than they were a few years ago

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POSTURAL HYPOTENSION WITH SYNCOPE

REPORT OF A CASE CURED WITH EPHEDRINE SULPHATE

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THE diagnosis of postural hypotension, as first described by Bradbury and Eggleston,¹ is predicated upon the following phenomena: (1) syncopal attacks on change of posture with a drop of the systolic blood pressure to the shock levels, (2) anhidrosis, (3) increased distress during the heat of the summer months, (4) slow and unchanging pulse rate with marked variation in the blood pressure, (5) slight decrease in the basal metabolic rate, (6) signs of slight and indefinite changes in the central nervous system, (7) blood urea at the upper normal level. Other relevant signs or symptoms in one or more of Bradbury and Eggleston's three cases were: (1) greater excretion of urine during the night than during the day, (2) loss of sexual desire and impotency, (3) a false general appearance of youth in comparison to the true age, (4) pallor of the skin and mucous membranes, (5) secondary anemia.

This condition must be differentiated from toxic vertigo, states of exhaustion, the Adams-Stokes syndrome, intracranial lesions, epilepsy and vestibular disease.

Until the appearance of the report of Ghrist and Brown,² the condition was not amenable to treatment. Their second case was relieved by ephedrine. In this connection the following case is reported because of the splendid response to the drug and complete relief for the past two years.

The theories as to the etiology of postural hypotension are admirably discussed by Bradbury and Eggleston¹ and Ghrist and Brown² and will not be gone into in this paper.

CASE REPORT

Mrs. H. M. S., an American farmer's wife, age 41, height 63 inches, weight 112 pounds, was referred by Dr. V. H. Mahan of New Lebanon, Ohio, on January 12, 1932, because of fainting spells and weakness. For the past 18 months she had been having attacks of syncope of increasing frequency and severity.³ The least exertion precipitated an attack, especially if in the upright posture. Weakness was gradual in development. Her vision was failing. She observed that the recumbent posture, when an attack impended, would lessen the severity. During the past summer perspiration was much less than usual for her. Particularly annoying was the increased frequency of urination at night. She complained also of gastric distress, aching in the muscles, a growing lack of energy and ambition, while the family noted a tendency to moodiness and despondency.

Her father was living and well at 71. Her mother had died at 67 of meningitis. Her husband was well at 46. Five brothers and five sisters were living and well.

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She had six children living and well. Two miscarriages occurred, 18 and 20 years before.

The patient was a definitely undernourished woman, appearing younger than the stated age, though pale and anemic looking. The teeth were good. The tongue was slightly coated. The thyroid was not enlarged. She was hyposensitive by Libman's classification. An orthodiascopic tracing of the heart revealed the following measurements: Great vessels 4.2 cm, MR 3.8 cm, ML 6.2 cm, total 10 cm. Internal diameter of the thorax 23 cm. Cardio-thoracic ratio 43 per cent. No murmurs were present. The lungs were normal. The skin was dry and the tissue turgor less than normal. No pigmentation was present. The abdomen and genitalia were normal. The deep and superficial reflexes were normal. A gastrointestinal examination was normal. Electrocardiograms in the upright and recumbent postures showed only the change due to shift of the axis. The basal metabolic rate was minus 14 per cent. The Wassermann and Kahn tests were negative. The urine was normal. The hemoglobin was 68 per cent (Dare), red blood cells 3,600,000, white blood cells 7,900, polymorphonuclear leukocytes 74 per cent, small lymphocytes 24 per cent and large lymphocytes 2 per cent. The blood urea was 46 mg, blood sugar 90 mg, calcium 9 mg, and non-protein nitrogen 32.5 mg, in 100 cubic centimeters of blood. The blood pressure recumbent was 130 systolic and 84 diastolic, pulse 46, erect, it was 84 systolic and 60 diastolic, pulse 24.

The following special tests were done, after Bradbury and Eggleston to check on the correctness of the diagnosis. Atropine, gr 1/60 subcutaneously produced no change in the pulse rate. Adrenalin, 1:1000 solution, 1 cc subcutaneously, elevated the pulse rate to 126 and caused nervousness and tremor. Pilocarpine, gr 1/10 subcutaneously, induced marked sweating and salivation.

The patient had been given various endocrine preparations, epinephrine, strychnine, etc., without benefit, but when her true condition was recognized, she was advised to take 25 mg of ephedrine sulphate every three hours (five doses per day). This dosage was continued for two weeks until January 26, 1932, when she was somewhat relieved, and then increased to 25 mg, each hour during the day. There then followed a remarkable improvement, and gradually the dose was lowered until in July 1932 it was discontinued and up to the present time none is needed. Her weight has increased from 112 to 156 pounds. The blood pressure phenomena are no longer present, she is able to do her own housework, the urinary symptoms have abated and the moodiness and despondency are relieved. At times she still complains of some general nervousness.

TABLE I
Effect of Posture on Urinary Output

| January 12, 1932 In bed Amount voided | Time | January 16, 1932 Up and about Amount voided |
|---|-----------|---|
| 125 cc | 8 a m | 20 cc |
| 105 | 9 | 15 |
| 90 | 10 | 30 |
| 160 | 11 | 30 |
| 140 | 12 noon | 10 |
| 110 | 1 p m | 70 |
| 135 | 3 | 105 |
| 110 | 5 | 60 |
| 85 | 7 | 90 |
| 1060 | Total day | 430 |
| 380 | Night | 1290 |
| 1440 | Day | 1720 |

TABLE II

Effect on Blood Pressure and Pulse Rate of Posture without Muscular Work

| Position | Time | Systolic blood pressure | Diastolic blood pressure | Pulse rate |
|----------------------------|-------|-------------------------------|--------------------------------|---------------|
| Horizontal | 10 12 | 130 | 84 | 68 |
| | 10 15 | 134 | 80 | 68 |
| | 10 20 | 84 | 64 | 24 |
| Head up, 40 degree angle | 10 24 | 80 | 58 | 65 |
| | 10 30 | 126 | 78 | 68 |
| Return to horizontal | 10 33 | 132 | 80 | 70 |
| | 10 36 | 172 | 108 | 64 |
| Head down, 40 degree angle | 10 39 | 169 | 106 | 68 |
| | 10 41 | 144 | 88 | 68 |
| Returned to horizontal | 10 45 | 140 | 84 | 70 |

SUMMARY

1 Postural hypotension with syncope is now a definitely recognized clinical entity

2 Three cases have been reported by Bradbury and Eggleston,¹ two by Ghrist and Brown,² two by Vaughn,⁴ one by Sanders,⁵ one by Riecker and Upjohn⁶ and the present case

3 No therapy was found of value until Ghrist and Brown reported the successful use of ephedrine sulphate in their second case

4 This is the second case benefited by the use of this drug and the change in the patient has been so marked that the word "cured" may be used advisedly in this instance

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AN EVALUATION OF THE USE OF QUINIDINE SULPHATE IN PERSISTENT AURICULAR FIBRILLATION *

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SINCE the introduction of quinidine therapy as a treatment of auricular fibrillation by Frey¹ in 1918, enthusiasm for its use has gradually waned. As with many new products in medicine early reports were very favorable, but careful observation over a period of years has shown that the use of the drug in permanent auricular fibrillation is warranted only in exceptional cases. It is indeed questionable whether any form of therapy to restore the normal rhythm is indicated in this condition.

Time has shown that restoration of normal rhythm by quinidine is not apt to be permanent and it becomes evident that mere reversion to normal rhythm is no criterion of the value of the drug. What is of more importance is the consideration of those patients who, over a long period of time, have maintained a sinus rhythm following quinidine. Are these individuals better off than a well digitalized fibrillator in whom the ventricular rate is slow and who exhibits little if any pulse deficit? Is the benefit which results from restoration of normal rhythm sufficient to outweigh the dangers incident to the use of quinidine? In 1925, Levine and Wilmaers² concluded, both from a theoretical point of view and from a clinical study of 38 cases of auricular fibrillation treated with quinidine sulphate at the Peter Bent Brigham Hospital, that much of the enthusiasm for the drug was unwarranted.

The present study is of 49 additional cases of auricular fibrillation treated with quinidine sulphate at the Peter Bent Brigham Hospital within the past seven years. Of this group, 46 were classified as permanent fibrillators and three as transient. In 35, or 71.4 per cent, of these cases normal rhythm was restored (Table 1). Of 33 cases with adequate follow-up notes, only 17, or 51 per cent, remained regular over one year, and as far as is known only one patient has maintained a normal rhythm for three years and in that case hyperthyroidism was one of the etiological factors for the fibrillation. With few exceptions, patients were hospitalized and kept under careful observation. Attempts were made to choose cases that seemed most suitable for the treatment. All patients were thoroughly digitalized and quinidine given only when it was felt that the patient was at his maximum point of improvement. In some cases, however, quinidine was given as a last resort and the fatal outcome of one case was probably contributed to by this procedure.

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† From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

TABLE I

| Etiology | Made Regular | Regularity Maintained | | | Failures | % Made Regular |
|-----------------------------------|--------------|-----------------------|-----------|---------|----------|----------------|
| | | under 1 yr | over 1 yr | unknown | | |
| Rheumatic | 15 | 7 | 8 | 0 | 10 | 60 |
| Hypertensive and arteriosclerotic | 2 | 1 | 1 | 0 | 2 | 50 |
| Postoperative hyperthyroid | 6 | 3 | 3 | 0 | 0 | 100 |
| Rheumatic and hyperthyroid | 4 | 2 | 2 | 0 | 0 | 100 |
| Chronic myocarditis | 5 | 1 | 3 | 1 | 2 | 71.4 |
| No demonstrable heart disease | 3 | 2 | 0 | 1 | 0 | 100 |
| Total | 35 | 16 | 17 | 2 | 14 | 71.4 |

Patients were given 0.2 gm of quinidine sulphate by mouth as a test dose. On the following day 0.3 gm was administered three times and each day the dose was increased 0.1 gm until the rhythm became regular or until some toxic manifestation made further administration of the drug seem unwise. In this way patients received 0.4 gm, 0.5 gm, 0.6 gm, and 0.7 gm three times a day on succeeding days. Occasionally it was necessary to go as high as 0.9 gm three times a day. When regular rhythm was established the patient was placed on a maintenance dose of 0.2 gm two or three times a day. Frequently it was necessary to increase the dose. One patient required a maintenance dose of 0.7 gm three times a day.

SEX

The sex of the individual was of little importance. This is the consensus of opinion of most observers^{3,4}. In our series there were 27 males and 22 females. Of the former, 18 were restored to normal rhythm and of the latter 17. There was apparently no relationship between sex and the duration of normal rhythm.

AGE

It has been pointed out by Weissman⁵ that age is not an important factor in the successful restoration of normal rhythm by quinidine. In his series more than 80 per cent of the patients in whom sinus rhythm was established were 50 years of age or over. Wolff and White⁴ state, however, that in their series, 80 per cent of the younger group whose ages ranged from 10 to 40 years were successfully treated, whereas in the older patients only 58.3 per cent were restored. They point out that age, so far as it has a bearing on the duration of heart disease, may be a factor of importance only in the cases of rheumatic disease with mitral stenosis. It was inferred that the duration of mitral obstruction might be directly related to the degree of auricular damage, the extent of which could hinder the restoration of normal rhythm. It must be remembered that auricular fibril-

lation is in most cases a late complication of heart disease and therefore a large percentage of the cases treated will be in older individuals

In our series only 17 of the 49 cases were under 40 years of age. Of these 17 cases, 10, or 58.8 per cent, were converted to a sinus rhythm. Of the 32 in which the ages were over 40 years, 25, or 78.1 per cent, were restored. The duration of normal rhythm, however, on the average was longer in the younger than in the older group

ETIOLOGY

Rheumatic heart disease, hyperthyroidism and hypertensive arteriosclerotic heart disease are the three chief etiological factors for auricular fibrillation. In almost 60 per cent of this series fibrillation was due to rheumatic valvular heart disease (table 1). Of the 29 cases so classified, 19 or 65 per cent, were restored to normal rhythm. All of the cases of hyperthyroidism when treated postoperatively responded to quinidine. In the non-valvular heart disease group, 63 per cent were converted to sinus rhythm. No heart disease was demonstrable in three cases and normal rhythm was established in all. Thus it would appear that the fibrillation due to rheumatic heart disease is less responsive to quinidine than are the other types. This is in agreement with the observations of Jamieson,⁶ Clark-Kennedy,⁷ Hay,⁸ and Viko, Marvin and White.³

Maynard⁹ stated that in mitral stenosis the maintenance of sinus rhythm was not satisfactory due to the extensive pathology. It is questionable whether or not the pathological lesion itself plays any definite part in the duration of fibrillation or in the duration of normal rhythm following quinidine. Frothingham¹⁰ in a pathological study of hearts of fibrillators and non-fibrillators found that there were no pathological changes common to all cases of auricular fibrillation. Nothing in his investigation indicated that the type of pathologic lesion found at autopsy could of itself be responsible for the onset and continuation of auricular fibrillation. Just as extensive lesions were to be found in both fibrillators and non-fibrillators.

Although all of the cases of hyperthyroidism treated with quinidine were converted to a sinus rhythm postoperatively in this study, only 66.6 per cent remained regular over six months. The resumption of auricular fibrillation in the minority of cases was probably due either to recurrent hyperthyroidism or some other form of independent cardiovascular disease.

DURATION OF FIBRILLATION

Duration of fibrillation is probably of some importance in quinidine therapy. One of the most difficult tasks facing the investigator of the problem of auricular fibrillation is that of obtaining an accurate history of the onset of the condition. In some individuals the sudden change in rhythm produces symptoms which when described are characteristic enough so that the onset may be accurately known. On the other hand, fibrillation

may exist for months and even years without the patient being aware of it. With these facts in mind, an approximation of the duration of fibrillation was made.

In table 2 it will be seen that the majority of patients had been fibrillating over six months. Of 19 fibrillating less than six months, 15, or 78 per cent, were restored to a normal rhythm, of 28 fibrillating over six months, 19, or 67.8 per cent, responded. Seven patients had a definite history of onset within a month before treatment was instituted. Of these, six were restored. Twenty patients had been fibrillating over one year and yet 15, or 75 per cent, were converted by quinidine. Thus we can draw no definite conclusions from these statistics as to the relative importance of duration of fibrillation to restoration of normal rhythm.

TABLE II

| Duration of Fibrillation | Number | Made Regular | Duration of Regular Rhythm | | | |
|--------------------------|--------|--------------|----------------------------|----------|-----------|---------|
| | | | under 6 mos | 6-12 mos | over 1 yr | unknown |
| Under 1 month | 7 | 6 | 2 | 1 | 3 | 0 |
| 1-6 months | 12 | 9 | 2 | 0 | 6 | 1 |
| 6-12 months | 8 | 4 | 2 | 0 | 2 | 0 |
| Over 1 year | 20 | 15 | 6 | 3 | 5 | 1 |
| Unknown | 2 | 1 | 0 | 0 | 1 | 0 |

More important than mere restoration of normal rhythm is the duration of normal rhythm. According to Viko, Marvin and White,³ in those patients in whom the duration of fibrillation was less than two months, not only was normal rhythm restored in a greater percentage, but it was also maintained to a much greater degree. They found, as was true in this study, that successful results could be obtained even though fibrillation had existed over 10 years. Our longest record of normal rhythm following quinidine was three years and this occurred in a patient who had been fibrillating for over two years. Thus it would appear that the duration of normal rhythm is not particularly influenced by the duration of fibrillation (table 2).

CLINICAL CONDITION OF THE PATIENT

The degree of congestive failure and the size of the heart have been considered decisive factors. Only one-fourth of those who had failure, but more than one-half of those who had not, maintained normal rhythm in the series reported by Viko, Marvin and White.³ Better results have been observed in patients with little or no cardiac enlargement.^{7,8} Of the 35 cases restored in this series, 25 had moderate to marked cardiac enlargement, 19 had objective signs of decompensation and 16 had a palpable liver (Tables 3 and 4). Of the 14 in which quinidine failed, 13 had moderate to marked cardiac enlargement, only one being normal in size. Fifty per

cent of these failures showed signs of decompensation. Since all of the cases were thoroughly digitalized prior to giving quinidine, it did not seem that the clinical condition of the patient, per se, was an important factor in the restoration of normal rhythm.

TABLE III

| Heart Size | X-Ray | | Percussion | |
|---------------------|--------------|----------|--------------|----------|
| | Made Regular | Failures | Made Regular | Failures |
| Not enlarged | 4 | 0 | 6 | 1 |
| Moderately enlarged | 3 | 1 | 12 | 6 |
| Markedly enlarged | 8 | 4 | 2 | 2 |

TABLE IV

| | Made Regular | Failures |
|----------------------------------|--------------|----------|
| Objective decompensation present | 19 | 7 |
| Objective decompensation absent | 16 | 7 |
| Palpable liver present | 16 | 9 |
| Palpable liver absent | 19 | 5 |

No constant ratio was found between the size of the heart, the clinical condition of the patient and the amount of quinidine necessary to convert to a normal rhythm. One case showing moderate cardiac enlargement and objective signs of congestive failure on admission, who had been a known cardiac of nine years' duration with fibrillation for two and a half months, responded to 20 gm of quinidine. Another patient whose onset of fibrillation occurred a few days before treatment was started and who showed no cardiac enlargement and but slight signs of decompensation, required 10.5 gm of quinidine.

AURICULAR FIBRILLATION VS. NORMAL RHYTHM

In considering the use of quinidine in chronic auricular fibrillation it must be emphasized that the drug does not influence the natural progress of the underlying disease, nor is there any indisputable evidence that it tends to increase the life expectancy of the patient. What then is the advantage of a normal rhythm in a heart which has adjusted itself to a fibrillating condition and can be adequately controlled with digitalis?

It is a common conception that a heart that is fibrillating predisposes to circulatory embarrassment. Stroud, LaPlace and Reisinger¹³ point out that "in terms of the physiology of the circulation it is really very questionable whether arrhythmia causes nearly as much circulatory embarrassment as one might, a priori, anticipate." It is indeed doubtful whether the well-digitalized, slowly fibrillating heart is not as efficient as the same heart converted to a normal rhythm. In the former condition the dangers incident to the use of quinidine are avoided.

Eyster and Swarthout¹⁴ working on dogs showed that fibrillation diminished the cardiac output by 40 per cent. However, animal experimentation cannot be considered reliable in discussing such a strictly clinical manifestation as auricular fibrillation. Blumgart and Weiss¹⁵ found that the circulation time in groups of patients with auricular fibrillation was prolonged from 75 per cent to 300 per cent. The prolongation was for the most part dependent upon the clinical condition of the patient at the time of the test. They stated that the prolongation of the circulation time was greater in proportion to the degree of decompensation than might be expected on the basis of determinations on similarly decompensated patients who showed a regular rhythm. The ideal test, however, would not consist of a comparison of similar cases but rather should be concerned with the improvement of circulation in the same individual following the production of a regular rhythm by quinidine. Certainly, the irregular rhythm at most plays only a small part in the prolongation of the circulation time and then only when the heart rate is in an uncontrolled state.

Lewis¹⁶ emphasizes the fact that it is the uncontrolled state of the heart in exercise which constitutes the most serious feature of fibrillation. Blumgart¹⁷ studying the effect of exercise on the fibrillating heart, found that the rise of rate in fibrillators was approximately double that of normal subjects and that there was a delayed return to the normal resting level. Neither the exaggerated rise of the ventricular rate in response to exercise, nor the delayed return is due to the abnormal mechanism of impulse formation, for it is also exhibited by the same patients when the rhythm has been restored to normal.

In most of the cases sinus rhythm produced by quinidine is not permanent, and even if permanent generally requires the continued use of the drug. Thus the old idea that making the rhythm regular by quinidine frees the fibrillating patient from further drug treatment in contrast to the indefinite use of digitalis, is a fallacy.

Levine and Wilmaers² found that the return to a sinus rhythm following the use of quinidine produced no change in the vital capacity of the lungs. They pointed out that whereas a fibrillating heart that becomes embarrassed can be made to respond to digitalis, that same heart with normal rhythm becomes a difficult therapeutic problem in the face of decompensation. It is evident that there is no definite proof that the chronic fibrillating heart when adequately digitalized so that the ventricular rate is slow and there is no pulse deficit, is less efficient than the heart restored to a sinus rhythm by the use of quinidine.

There is one condition in which obtaining a regular rhythm of the heart beat may be of distinct value. Those fibrillators whose chief complaint is a tumultuous beating of the heart even when adequately digitalized, are frequently strikingly improved when restored to normal rhythm. This is not invariably true and Stroud, LaPlace and Reisinger¹⁸ state that the majority of their cases were no less "heart conscious" with restored sinus

rhythm than during the period of their fibrillation under effective digitalis therapy

In the Cardiac Clinic at the Peter Bent Brigham Hospital, quinidine as a prophylactic measure has been used to prevent the onset of fibrillation. It is logically indicated in cases such as rheumatic heart disease with mitral stenosis where the development of frequent extrasystoles presages the onset of fibrillation. Small doses of quinidine sulphate often cause the disappearance of this irregularity and continued use of the drug may possibly be delaying the development of the inevitable state of fibrillation. It would also appear to be indicated in small doses in cases which will inevitably fibrillate even though there are no signs or symptoms suggesting that fibrillation is imminent.

AURICULAR FIBRILLATION AND AURICULAR THROMBI

That auricular fibrillation predisposes to the formation of clots in the auricles has clinically been generally accepted. Lewis¹⁶ found that in 76 autopsies on cases dying of chronic heart disease, in which thrombi were especially sought for, they were present in eight out of 23 in which fibrillation was present in the last illness and in only four out of 53 in which the mechanism had been normal. Harvey and Levine¹⁸ in a study of mural thrombi found that in 31 cases of persistent auricular fibrillation, all but three had auricular thrombi (90 per cent). Of the other 80 cases in their series that showed thrombi but did not show auricular fibrillation only 43 had auricular thrombi (54 per cent).

Appreciating that fibrillators are in general older than non-fibrillators, the distinction between the effect of aging or duration of the disease and that of the arrhythmia itself in the production of thrombus formation has not been clearly made. An analysis was therefore made of 62 necropsy protocols of mitral stenosis cases at the Peter Bent Brigham Hospital covering a period of 15 years. From a statistical standpoint it was found that similar figures were obtained regardless as to whether the lesion was a pure mitral valve involvement or whether both mitral and aortic valves were diseased. There were 34 fibrillators and 28 non-fibrillators. Auricular thrombi were present in 20 of the fibrillators (58.8 per cent) and in only four of the non-fibrillators (15 per cent). They were present in the right auricle in eight cases, in the left auricle in six, and in both auricles in ten. Thrombi were most frequently found in those cases in which fibrillation had been present for over six months (table 5).

The average age of cases with auricular thrombi was from 10 to 15 years greater than those in which thrombi were not found. It must not be inferred from this that it is advantageous for these cardiacs to have mural thrombi, but rather that if they are fortunate enough to live longer, there is greater likelihood that mural thrombi will form. Of nine cases in whom the age was over 40 and fibrillation not present, four showed auricular

thrombi (average age 50 years) In the same age group in which fibrillation was present 12 out of 15 cases showed auricular thrombi (average age 49 years) This indicates that fibrillation apart from the aging factor is conducive to thrombus formation That age, or possibly duration of the disease, is an additional factor is shown by the fact that there were no instances of thrombus formation in non-fibrillators under 40 years and only eight instances in 19 fibrillators in the younger group Thus one must concede that the presence of fibrillation and the increasing years are both separate factors favoring auricular mural thrombosis

It is Lewis' impression, however, that embolism due to detachment of the thrombi was not more common when the heart was fibrillating than when the action was normal He feels that "while fibrillation predisposes to clotting, the normal auricular action favors the detachment of such clots" ¹⁶ Apparently the sudden onset of normal rhythm is an important factor in the production of emboli MacKenzie ¹⁹ called attention to the fact that embolism occurs frequently when the rhythm spontaneously changes from fibrillation to normal The not infrequent occurrence of embolism

TABLE V
Mitral Stenosis with Fibrillation

| Case | Sex | Age | Duration of Fibrillation | Location of Thrombus | Other Valve Lesions |
|------|-----|-----|--------------------------|----------------------|---------------------|
| 1 | F | 23 | 7 years | No thrombus | None |
| 2 | F | 68 | 1 year | Lt auricle | " |
| 3 | M | 21 | (?) | No thrombus | |
| 4 | F | 66 | 2 years | No thrombus | |
| 5 | F | 31 | (?) | No thrombus | |
| 6 | F | 17 | Recent | No thrombus | |
| 7 | F | 55 | 4 years | Rt auricle | " |
| 8 | F | 60 | (?) | No thrombus | |
| 9 | F | 42 | 3 years | Lt auricle | " |
| 10 | M | 18 | 1 week | Rt auricle | |
| 11 | F | 43 | 5 years | Rt auricle | |
| 12 | F | 46 | 1 week | Rt auricle | |
| 13 | F | 40 | (?) | Rt auricle | |
| 14 | F | 27 | 1 week | No thrombus | Aortic |
| 15 | F | 39 | 2 years | Rt and Lt auricles | " |
| 16 | M | 16 | 1 week | No thrombus | |
| 17 | F | 48 | 10 years (Par) | Rt and Lt auricles | |
| 18 | F | 17 | 3 years | No thrombus | |
| 19 | F | 27 | 1 year (Par) | No thrombus | |
| 20 | F | 18 | 6 days | No thrombus | |
| 21 | F | 51 | (?) | Rt and Lt auricles | " |
| 22 | F | 32 | 7 years | Lt auricle | |
| 23 | F | 75 | (?) | No thrombus | |
| 24 | M | 45 | 3 years | Rt and Lt auricles | " |
| 25 | M | 32 | 2 years | Rt and Lt auricles | " |
| 26 | F | 17 | Recent | No thrombus | |
| 27 | M | 29 | Several years | Rt and Lt auricles | " |
| 28 | F | 39 | 1 year | Rt and Lt auricles | " |
| 29 | F | 47 | 6 years | Rt and Lt auricles | " |
| 30 | F | 36 | 3 years | Rt auricle | |
| 31 | M | 44 | 3-4 years | Lt auricle | |
| 32 | M | 22 | (?) | No thrombus | |
| 33 | M | 53 | (?) | Rt auricle | |
| 34 | F | 45 | 14 months | Lt auricle | " |

TABLE V—Continued
Mitral Stenosis without Fibrillation

| Case | Sex | Age | Duration of Fibrillation | Location of Thrombus | Other Valve Lesions |
|---|-----|-----|--------------------------|----------------------|---------------------|
| 35 | F | 55 | | No thrombus | None |
| 36 | M | 24 | | No thrombus | " |
| 37 | F | 14 | | No thrombus | " |
| 38 | F | 12 | | No thrombus | " |
| 39 | M | 40 | | No thrombus | " |
| 40 | M | 44 | | Lt auricle | " |
| 41 | F | 52 | | No thrombus | " |
| 42 | M | 59 | | No thrombus | Aortic |
| 43 | M | 38 | | No thrombus | " |
| 44 | F | 58 | | No thrombus | " |
| 45 | F | 58 | | Rt and Lt auricles | " |
| 46 | M | 58 | | Rt and Lt auricles | " |
| 47 | M | 28 | | No thrombus | " |
| 48 | M | 26 | | No thrombus | " |
| 49 | F | 13 | | No thrombus | " |
| 50 | F | 19 | | No thrombus | " |
| 51 | F | 41 | | Rt auricle | " |
| 52 | F | 16 | | No thrombus | " |
| 53 | F | 24 | | No thrombus | " |
| 54 | F | 15 | | No thrombus | " |
| 55 | M | 17 | | No thrombus | " |
| 56 | F | 13 | | No thrombus | " |
| 57 | M | 23 | | No thrombus | " |
| 58 | M | 40 | | No thrombus | " |
| 59 | M | 37 | | No thrombus | " |
| 60 | M | 14 | | No thrombus | " |
| 61 | M | 16 | | No thrombus | " |
| 62 | F | 59 | | No thrombus | " |
| Average age of patients with mitral stenosis with auricular fibrillation | | | | | 37.0 |
| Average age of patients with mitral stenosis without auricular fibrillation | | | | | 32.6 |
| Average age of patients with mitral stenosis with auricular fibrillation and with auricular thrombi | | | | | 42.5 |
| Average age of patients with mitral stenosis with auricular fibrillation and without auricular thrombi | | | | | 31.2 |
| Average age of patients with mitral stenosis without auricular fibrillation and with auricular thrombi | | | | | 50.2 |
| Average age of patients with mitral stenosis without auricular fibrillation and without auricular thrombi | | | | | 29.6 |

at the time of, or at least soon after, the restoration of sinus rhythm tends to further support this point. When one considers that certain thrombi are exceedingly small and frequently tend to form in the extreme tips of the auricle, it will become obvious why the initial contractions of the auricle may fail to dislodge an embolus. The embolus may become dislodged a few months later from the constant auricular systole weakening the thrombus and eventually causing a part of it to become separated.

In 1923, Viko, Marvin and White² compared the frequency of embolism and other untoward results under quinidine in 484 reported cases of fibrillation with the frequency of embolism in 200 consecutive cases of auricular fibrillation at the Massachusetts General Hospital not receiving quinidine. During the short period of quinidine treatment in these 484 cases, embolism occurred in 15, or 3.1 per cent. In the 200 cases not treated with quinidine and presumably treated with digitalis, embolism occurred in 16, or 8.0 per

cent They concluded that embolism is not much more frequent under quinidine treatment than under ordinary therapy An analysis of these figures leads us to believe that the comparison is hardly valid Embolic phenomena during quinidine administration usually occur at, or shortly after, the restoration of normal rhythm, or in exceptional cases before sinus rhythm is established If emboli result from the use of quinidine they do so usually during the first 10 days of treatment Thus in the 484 quinidine treated cases, the active therapy covered only some 4,840 days The duration of treatment with digitalis is generally much longer, a reasonable average being one year per patient or about 70,000 days for the 200 cases Certainly that drug which causes as many instances of embolism in 4,840 days as another in 70,000 days is the more dangerous In fact the occasional embolism during long digitalis administration may be regarded as an inevitable accident of heart disease but when it occurs under quinidine therapy in most instances, it is actually precipitated by that drug

UNTOWARD EFFECTS

Various observers have reported innumerable types of toxic manifestations following the use of quinidine sulphate With the exception of those cases in which normal rhythm is restored by small doses of the drug, symptoms of quinine intoxication are the rule The most frequent of these are nausea, vomiting, epigastric distress, diarrhea, headache, palpitation, tinnitus, fever, mental depression, flushing, sweating, syncope and a feeling of apprehension Skin manifestations including papular, scarlatiniform rashes, urticaria and inflammatory edema of the face have been reported Symptoms such as transient attacks of failing or blurring of vision are occasionally encountered Cerebral symptoms associated with diplopia and extreme excitability may result

The induction of heart failure has been reported several times²⁰⁻²¹ It is thought that this is due to the accelerated ventricular rate The latter results both from vagal paresis and from the increased number of stimuli reaching the ventricle as the result of the slowing of the auricular rate Carr and Spoenman,²² adopting a rate of 130 as a limit calling for the withdrawal of quinidine, reported discontinuance of the drug for this reason in 11 cases out of 87 treated The direct poisonous effect of quinidine upon the myocardium must also play some part in this effect

Cases of sudden and temporary collapse with loss of consciousness and failure of respiration are occasionally encountered Sudden death not embolic in nature has been frequently reported Various explanations have been offered for this phenomenon including ventricular fibrillation, cardiac asystole due to failure of the S-A node to function when fibrillation ceases, heart block and marked vagal stimulation White²³ suggests that the possibility of standstill of the whole heart due to depression by quinidine of the ventricular as well as the auricular pacemaker should also be considered

Respiratory paralysis has also been reported Schott²⁸ reproduced this quinidine effect in dogs and Gordon, Matton and Levine,²⁹ in cats It is probable that this occurs more frequently in human cases than has been appreciated

In this series of cases, three fatalities occurred during therapy In two of the instances it was felt that the patients' death was an event that might have been postponed for a matter of years had they been treated with digitalis and had no attempt been made to regularize the rhythm One was a 44 year old female with rheumatic heart disease and mitral stenosis The onset of fibrillation occurred in this hospital 10 months before the patient's death The use of quinidine one month after the onset of fibrillation successfully restored sinus rhythm The patient showed little subjective improvement but continued with a normal rhythm until a few days before her last admission, when, despite a maintenance dose of 0.2 gm of quinidine sulphate, twice daily, she reverted to the fibrillating state At this time she had no objective or subjective cardiac decompensation The heart was not enlarged and although fibrillating for the second time, the onset could certainly be considered as "recent" She was digitalized and quinidine was given in the routine manner On the seventh day she received 0.8 gm three times during the day but continued to fibrillate Early the following morning she suddenly groaned and was dead Necropsy revealed a thrombus in the left auricle but no evidence of emboli

The second case was a 20 year old male with rheumatic mitral stenosis and insufficiency The onset of fibrillation dated back about one and one-half years, shortly after which time he was restored to a sinus rhythm by the use of quinidine He remained regular for one year and then reverted to fibrillation despite a maintenance dose of 0.2 gm of quinidine daily His rhythm was again made regular and remained so for about six months With the last onset of fibrillation it was decided to attempt to obtain a regular rhythm with the patient ambulatory as his condition was quite good and there was no evidence of decompensation Quinidine was administered in the usual manner The day before his death the heart became regular, the last dose of quinidine administered being 0.8 gm The following morning he arose and appeared to be feeling very well and his heart rhythm was regular While resting that morning he suddenly gasped, became cyanotic and respirations ceased No autopsy was obtained

The other case might be considered as a poor risk He was a 64 year old male with chronic myocarditis and fibrillation of approximately six months' duration His heart was enlarged and on admission there was marked congestive failure with a liver palpable 4 cm below the costal margin Digitalis was administered but discontinued because of marked coupling of the pulse beat Quinidine was then started and after having received 2.8 gm in a period of 72 hours, the patient suddenly became dyspneic and unconscious His heart was beating regularly and at a rate of 80 beats per minute There was no motor paralysis The attack was relieved by caffeine sodium

benzoate and examination one-half hour later showed a gross irregularity. Thirty minutes later the patient again became dyspneic and the heart beat exhibited a bizarre form of arrhythmia with varying periods of irregularity and regularity, occasionally slow and at other times fast. Suddenly no heart sounds were to be heard and after three minutes adrenalin was administered intracardially. The patient responded to such an extent that 30 minutes later the pulse was regular with a rate of 100. He had several more such attacks and although he responded for a while to stimulation, finally succumbed 80 hours after the onset of therapy. No autopsy was obtained.

It has been our experience at the Peter Bent Brigham Hospital that all cases of sudden death in which it seemed that quinidine was the cause have occurred in patients with mitral stenosis. This includes the two above-mentioned cases and three previously reported.² A review of the cases reported in the literature does not reveal this to be invariably so but it is true in the large majority of such cases. Thus we are inclined to agree with other investigators who consider long-standing valvular heart disease to be a contraindication to the use of quinidine.

Other various toxic phenomena occurred during the administration of quinidine. There were four instances of cerebral emboli, all recovering. One case of pulmonary infarction developed. Symptoms of emchionism sufficient to require discontinuance of the drug occurred in eight cases and severe precordial pain resulted in three cases.

QUINIDINE THERAPY IN FIBRILLATION DUE TO HYPERTHYROIDISM

In those patients in whom hyperthyroidism is the etiological factor for fibrillation, quinidine sulphate is an ideal drug after the hyperthyroidism has been cured and provided there is no other cardiac involvement of an organic nature. When there is in addition to the hyperthyroidism a rheumatic involvement of the heart, the etiological factor for the fibrillation is often the rheumatic lesion rather than the disturbance of thyroid function. The use of quinidine in an undamaged heart is probably a safe procedure, when myocardial or endocardial involvement is present, the same hazards discussed above obtain.

Quinidine should be administered only postoperatively and then only after a reasonable time has elapsed to permit spontaneous return to sinus rhythm. Two to three weeks is a sufficient test period although shorter periods have been suggested. Anderson¹¹ believes that if auricular fibrillation recurs after quinidine has been administered postoperatively, residual or recurrent hyperthyroidism may always be suspected. In these cases one should also search carefully for some other etiological factor for the fibrillation. The addition of quinidine therapy following thyroidectomy when auricular fibrillation is present will restore normal cardiac rhythm in over 95 per cent of the cases. Hurvath¹² states that if the hyperthyroidism is uncomplicated by cardiovascular disease, a return to normal rhythm may be anticipated in practically 100 per cent of the cases.

In all of the six cases of hyperthyroidism in our series treated post-operatively, and in four additional cases of hyperthyroidism complicated by rheumatic heart involvement and treated following subtotal thyroidectomy, a return to normal rhythm was obtained (table 1). Of the pure hyperthyroid cases three maintained normal rhythm over six months, two less than six months and no follow-up was available in one case. Of the four cases of rheumatic heart disease and hyperthyroidism, two remained regular over six months and two less than six months.

INDICATIONS AND CONTRAINDICATIONS

A consideration of cases regarded by investigators as unsuitable for quinidine therapy reveals that in chronic auricular fibrillation there remains only a small group in which the drug should be used. An idiosyncrasy to quinine and a previous history of embolism are universally agreed to be contraindications. Badly damaged hearts with long standing valvular disease, and more particularly if there is undoubted failure of compensation with venous engorgement, are considered unfavorable factors. The use of the drug is regarded as hazardous when there is severe myocardial damage even without decompensation. When angina pectoris has been relieved by the onset of fibrillation one should hesitate to convert the rhythm to normal and again subject the patient to anginal pain. Acute or subacute infective endocarditis, fibrillation with complete heart block, aortic disease, active hyperthyroidism, and the presence of chronic interstitial nephritis, all have been pointed out as contraindicating quinidine therapy.^{8, 9, 12, 24, 25, 26, 27} Spiro and Newman²⁶ state, "it is almost useless to give a patient quinidine if he has auricular fibrillation and hypertension." Marked cardiac hypertrophy and long standing fibrillation are also considered unfavorable conditions. Some of these contraindications are obvious, but as to others one might readily take exception.

What then are the indications for the use of quinidine sulphate in chronic auricular fibrillation? One is forced to weigh the benefit derived by the patient as a result of making his heart rhythm regular against the danger incident to the use of the drug. There should be assurance that the patient will be objectively and subjectively in better health than if he were adequately digitalized and fibrillating with a slow ventricular rate.

Quinidine may be used with fair safety in cases in which the heart is normal. It is of distinct value in postoperative cases of hyperthyroidism uncomplicated by cardiovascular disease, and when sufficient observation has shown that a spontaneous return to normal will not occur. In certain carefully selected cases whose chief complaint is intractable palpitation even after adequate digitalis has been administered, quinidine treatment may be warranted. We are inclined to believe that quinidine is occasionally indicated in certain otherwise hopeless cases where all other means have failed to produce a response. Such situations are well illustrated by the extremely gratifying results obtained in the following two

Van Nuys³⁰ reported a case of fibrillation in a male, 64 years of age who had dyspnea, edema, cough and precordial pain despite large doses of digitalis. The heart was moderately enlarged and there was objective decompensation with an apex rate of 160 to 190. The patient became progressively worse despite ordinary therapy and as a last resort he was hospitalized and quinidine was given. After 4.4 gm of the drug the heart rhythm became regular, but remained so only on a daily dose of 1.6 gm. During the period of experimentation he steadily improved despite frequent returns of arrhythmia, thus it is possible that the mere hospital routine played a part in his improvement. However, the quinidine dosage was gradually reduced and finally discontinued. He continued with a normal rhythm and was able to lead a quiet life feeling as well as he did before the onset of symptoms one year previously.

We had a similar case in our series. The patient was a 64 year old physician with hypertension and chronic myocarditis who had been a known fibrillator for five years. For one and one-half years before admission he had been having frequent attacks of angina pectoris and occasional nocturnal dyspnea. On admission he was cyanotic and orthopneic. The heart was enlarged and there were signs of marked congestive failure including edema, an enlarged liver and pulmonary congestion. He was irrational and breathing was of the Cheyne-Stokes type. Digitalis was given until toxic symptoms intervened when it was discontinued and quinidine therapy instituted. Although there was slight betterment of his condition before quinidine was given, a regular rhythm, following 2.5 gm of the drug, produced almost miraculous response. Following his dismissal from the hospital, the patient again took up the practice of medicine and when last seen two and one-half years later was in good health with a regular heart rhythm and still conducting his medical practice.

SUMMARY

An analysis was made of 49 cases of auricular fibrillation treated with quinidine sulphate. From observations made on these cases and from a review of the literature, the following conclusions can be drawn:

- 1 The question of reversion to a normal rhythm is not the only criterion necessary to judge the success of the treatment.

- 2 Sex is of no importance in this problem and age enters into consideration only in so far as older patients are somewhat more apt to have mural thrombi.

- 3 From an etiological point of view, rheumatic valvular disease is most resistant, non-valvular fibrillation responds more readily and in cases of hyperthyroidism without cardiovascular disease treated postoperatively, reversion to normal rhythm is practically invariable.

- 4 Duration of fibrillation influences to some extent the likelihood of reversion. Those cases in which there is a short history of fibrillation revert

more readily. A longer duration of fibrillation is more frequently attended with the presence of auricular thrombi and the danger of peripheral emboli.

5 The clinical condition of the patient proved to be no guide in avoiding disastrous results.

6 It is doubtful whether most cases are in better health with a regular rhythm than with auricular fibrillation when the ventricular rate can be kept slow.

7 An analysis of 62 autopsied cases of mitral stenosis has been made and statistical evidence is presented to prove that auricular thrombi are more frequent in fibrillating than in non-fibrillating hearts. It has been shown that the presence of fibrillation and increasing years are both separate factors favoring auricular mural thrombosis.

8 There seems to be no method of predicting the dire accidents that attend quinidine therapy such as sudden death and emboli for they occurred in patients who had been regarded as most favorable for quinidine treatment.

9 The four indications for the use of quinidine sulphate in chronic auricular fibrillation seem to be (a) the presence of fibrillation in an otherwise normal heart, (b) its persistence after operation for hyperthyroidism, (c) when the irregularity is the cause of intractable palpitation and (d) in certain hopeless cases where other forms of treatment have failed.

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TRICHINOSIS

A REPORT OF EIGHT CASES WITH SKIN AND PRECIPITIN TESTS '

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PRIOR to 1928, a diagnosis of trichinosis was usually made by microscopic examination of tissue removed from a patient whose symptoms and blood picture had suggested that possibility. The utility of the skin and precipitin tests developed by Bachman in that year has been remarked by several later observers, and this report adds further confirmatory evidence regarding the accuracy and sensitivity of these tests.

The disease occurs more commonly than is generally known. The United States Public Health Service for the year 1932 reported 263 cases from 15 states. For the first nine months of 1933, 13 states reported 208 cases of trichinosis. From 1921 to 1928 the annual deaths from trichinosis in the registration area averaged 14 per annum. New York and California report more cases than any other states.

The New York State Department of Health in November 1933 reported in upstate New York 39 cases for the year 1930, 57 cases for 1931, and 21 cases for 1932. In the first 10 months of 1933, 74 cases were reported. This is three times the number of cases of the preceding year. In my own county (Suffolk, New York) no cases were reported in the last four years.

In regard to the general incidence of trichinosis, reported and unreported, it may be noted that Williams in 1901 reported an incidence of 5.34 per cent of trichinosis in 505 autopsies. In 1931, Queen, in 344 routine autopsies in Rochester, New York, found 17.5 per cent positive by a digestion method of examination of the diaphragm muscle. More extensive use of the Bachman tests will undoubtedly reveal many cases of this disease which would otherwise have remained undiagnosed.

The cause is the *Trichinella spiralis*. The mode of infection is through the ingestion of raw or insufficiently cooked pork. The carriers are the hog and the rat, and infection in mankind is accidental and does not result in further infestation. The trichinella is liberated when the trichinous wall is digested in the stomach and the fertilized female liberates the embryo into the lymph spaces of the mucosa of the intestines. From thence they go to the blood and are distributed to the muscles. The worm has been found in the spinal fluid, blood, stool and muscle.

There are three stages. The first or infestive stage is immediately followed by vomiting, diarrhea or constipation, and abdominal pains with hyperpyrexia. There are also muscle pains and prostration. The second

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stage is due to the invasion of the blood stream and is characterized by edema of the face and eyelids, less elevation of temperature, swelling of muscles, bronchitis and prostration. This period lasts about three weeks. The third stage is the stage of encystment, which occurs within the fifth and sixth weeks and is characterized by weakness and edema of the face and extremities. The temperature is usually normal.

The disease has been mistaken for typhoid fever, chronic rheumatism, sinusitis, gripe, acute nephritis and other diseases. The characteristic laboratory finding that usually calls attention to the diagnosis is eosinophilia, sometimes as high as 60 per cent or more. In the early stages with extreme hyperpyrexia there may be leukocytosis without eosinophilia. The treatment is symptomatic, and although many drugs are recommended, it is generally believed that none is specific. Salzer has reported curative action with convalescent serum, but this has been contradicted.

CASE REPORTS *

Of the eight cases here reported five occurred in one group. These five patients were employed in one institution, and ate their meals together. Of the other three cases, two were in the same family (mother and son). The third, as far as is known, was not connected with other cases.

First Group

As noted above, these five patients ate their meals together. Apparently the food ingested was thoroughly prepared, the pork being fried or broiled, and when at times sausages were eaten these were well baked. Moreover, three other girls partook of the same food at all times, only one of whom developed symptoms. This institution catered to about 50 guests, none of whom became ill. A possible explanation for this may be that the guests ate after the employees, and in this way the pork and sausages they consumed had been given additional baking or frying.

CASE I

J. W., female, white, aged 25, occupation, cook. This patient came into my office on September 24, 1933, complaining of swelling of the eyelids and of a burning sensation in both eyeballs. The lids were so edematous that it was painful to open and close the eyes and the eyelids were so tight that the upper eyelid could not be everted. Her temperature was normal and she had no other symptoms. Three days later she had a temperature of 101° F. and complained of marked weakness, pain in the neck muscles and general bodily aches and pains. She continued to complain of swelling of the eyelids. A blood count on October 2 showed WBC 7,600, PMN's 49 per cent, P M E's 25 per cent and lymphocytes 26 per cent. The stools were negative for parasites. Another differential count on October 3 showed the following: PMN's 64 per cent, P M E's 18 per cent, and lymphocytes 18 per cent.

* In the preparation of the following cases I wish to thank Dr. A. Angrist and Dr. W. H. Ross for their kind assistance. I also wish to thank Mr. R. Smith of the Southside Hospital Laboratory, and the New York State Laboratory for their assistance.

She was ordered to bed and her temperature varied from 100° to 101° F. Gradually the fever subsided so that she was able to go to work after 11 days. Even while working she still complained of swelling of the ankles, weakness of the thighs and legs, and swelling of the eyelids for another two weeks until she fully recovered.

CASE II

M. B., female, white, aged 25, occupation, maid. The onset of her illness was on September 24, when she complained of swelling of the eyelids, weakness, and fever (of 101° F). She was sent home and did not ask for medical care until September 27 when she came into my office, complaining of swelling of the eyelids, upper part of the face and lips. She had no fever at that time, and complained of a sore throat. She said that she felt as though she had a cold. Physical examination was essentially negative. A differential count showed the following: P M N's 31 per cent, P M E's 48.3 per cent, and lymphocytes 19.7 per cent, large mononuclears 0.7 per cent.



FIG. 1. Patient M. B. *Trichinella spiralis* in hemolyzed blood. High power.

A microscopic examination of blood hemolyzed in 3 per cent acetic acid, revealed *Trichinella spiralis* (Figure 1). She continued to have a low grade fever from 100° to 101.5° F daily, complaining of weakness, pains in the muscles of the calves of the legs, and swelling of the ankles, until October 16 when she returned to work. Since then her course has been uneventful.

CASE III

G. S., female, white, aged 21, occupation, waitress. This girl was sent home from work on September 27 because of swelling of the face and eyelids. She had a fever of 101° F. I saw her two days later, and she presented the same picture. She also complained of weakness, backache, and that the muscles of her jaw were painful.

She felt as though she had a toothache. She had vomited twice, but had had no diarrhea. There was pain on flexion of the head backward or forward, and intense headache aggravated by any movement. There was a positive Babinski sign on the right side and both knee jerks were elicited with difficulty. A blood examination on October 1 showed RBC 4,800,000, Hgb 90 per cent, WBC 9,000, PMN's 44 per cent, P M E's 37 per cent, and lymphocytes 19 per cent.

She continued to have a low grade fever, and on October 4 small nodules appeared on the extensor surfaces of both forearms just above the wrists, they were about the size of a 10 cent piece and were surrounded by an inflammatory areola. These nodules (one on each forearm) disappeared in 24 hours. On October 7 she became very ill, her temperature reached 104° F and she complained of severe pains and aches all over her body. She had a harsh cough and both lungs revealed bronchitis with coarse rales throughout. A blood count on that day showed WBC 21,000, PMN's 56 per cent, P M E's 13.3 per cent, and lymphocytes 30.7 per cent.

Examination of stool on October 9 was negative for parasites and stool cultures were negative for typhoid. She continued to have a high fever for several days. The swelling of the eyelids and face gradually disappeared, and the bronchitis improved. The temperature became normal and on October 16 she returned to work. She felt weak for the following month, complaining of muscle aches and pruns and swelling of the ankles until she gradually recovered.

CASE IV

H L, female, white, aged 23, occupation, second cook. On September 29 she became ill, complaining of swelling of the eyelids and face, and aches and pains all over her body. She felt very weak, had an intense headache and experienced difficulty in moving her jaw. She had vomited twice but had no diarrhea and no abdominal pain. Her temperature was 101° F. On October 3 a differential count revealed PMN's 59 per cent, P M E's 29 per cent, and lymphocytes 12 per cent. Another blood count on October 6 revealed PMN's 50.5 per cent, P M E's 27 per cent, lymphocytes 20.5 per cent, and large mononuclears 2 per cent. A specimen of blood was tested for agglutination with *B abortus* and was negative. A Widal showed a doubtful reaction which was probably due to the patient having had typhoid vaccine previously. Her temperature was about 101° F. On October 9 when she returned to work she had improved a great deal, her temperature was normal but she still had a fine tremor of the hands and a slight urticarial eruption on the arms.

After she returned to work she still had several episodes of illness. On October 14 she vomited twice and felt very weak. When seen on October 22 she complained of pruns in the calves of the legs, tremor, and nightmares.

She had lost 10 pounds. On October 28 she still complained of swelling of the ankles and calves. She had morning headaches and her eyes appeared bloodshot. She continued working, however, and made a steady improvement.

CASE V

G H, female, white, aged 24, occupation, chambermaid. On October 1 the patient complained of slight swelling of the eyelids, weakness and muscle pains. She had an intense headache and prun on flexing or extending the head. Her temperature was normal. The following day her entire face became swollen, especially the upper lip, so that her appearance was quite alarming. She developed an urticaria of the entire body which became more prominent or faded, advanced or receded from day to day, lasting for several days. This patient had been seen about a month previously when she had had a slight urticaria and had been cautioned against eating meats. In spite of this she had taken a small amount of pork occasionally. On October 3 a

blood count showed P M N's 66 per cent, P M E's 19 per cent, and lymphocytes 15 per cent. Another blood count on October 6 revealed P M N's 52.5 per cent, P M E's 14.5 per cent, lymphocytes 30.5 per cent, and large mononuclears 2.5 per cent. No agglutination was obtained with *B. abortus* and the Widal reaction was doubtful (This patient had also had typhoid vaccine previously). She continued to complain of muscle pains and weakness and ran a low grade fever, 100° to 101° F, until October 16 when she felt well enough to return to work. I saw her a week later on October 22, and she still complained of pains and weakness in the knees and dizziness when lying down. Her temperature was normal. On October 28 she still had slight weakness, her arms ached occasionally, but she felt much better. Thereafter she continued to improve and made a gradual recovery.

Second Group

CASE I

P. K., male, white, school boy, aged 16 years. This patient was first seen on October 10, 1933. He complained of pain on moving his neck forward or backward, and his eyelids were swollen. He looked extremely toxic and had a temperature of 104° F. Physical examination revealed coarse bronchial râles anteriorly. He had a suggestion of a positive Kernig sign of both lower extremities. His symptoms suggested some meningeal or encephalitic lesion, but on account of the swelling of the eyes and the history of coincidental sickness of the mother who also had swelling of the eyelids, a blood count was taken which showed a marked eosinophilia of 25 per cent. The boy felt much better the following day. His temperature was only 101° F, and although he still had swelling of the eyelids and pains in the calves of the legs, the other signs were gone. He continued to improve and on October 17 his temperature was normal. He still felt extremely weak, however, and had generalized muscle and joint pains, especially in the muscles of the calves of his legs. On October 23 while attending school he noted that both his hands were swollen and large nodules appeared above the wrist on the dorsum of each forearm. A blood count on that day showed P M N's 37.7 per cent, P M E's 46.7 per cent, P M B 0.3 per cent, lymphocytes 14.3 per cent, and large mononuclears 1 per cent.

The swellings of the hands and wrists disappeared within 24 hours, and the patient recovered without further complications. A biopsy from the calf muscle was negative for *Trichinella spiralis*.

The family denied eating pork, but gave a history of having eaten sausages the week prior to the onset of the illness. These sausages were bought from a chain butcher shop, and were apparently fairly well cooked.

CASE II

M. K., female, white, housewife, aged 60, mother of P. K., the foregoing case. This patient became ill about October 6. She had severe diarrhea and swelling of the eyes for three or four days. She had pains in all her muscles, especially in the calves of the legs, and her ankles were swollen. On examination on October 10 she had a fever of 101° F. She had paid no attention to her symptoms and thought that she had "grippe." The presence of eosinophilia in her son's blood caused a blood count to be taken and her blood also showed 25 per cent of eosinophiles. This patient was not as sick as her son and made a quicker recovery, the entire illness lasting only about one week. An interesting point was that the father who takes a glass of liquor with his meals and who also ate the sausages, had no symptoms.

Third Group

CASE I

F. M., male, white, aged 32, married, occupation, iceman. This patient dates his illness to October 16 on which day he ate some pork chops in a lunch wagon; he mentioned afterward that they were not well done. He has also been in the habit of eating uncooked pork salami. On October 17 he complained of headaches, swelling of the eyes and extreme weakness. He had severe pains in the muscles of the back. I first saw him on October 19, and his entire face looked swollen, especially the eyelids. He had difficulty in extending and flexing the head. He had a fever of 101° F. He also mentioned that he had taken several aspirin tablets for a very intense headache, without relief. A blood count on October 20 showed P. M. N.'s 70 per cent, P. M. E.'s 10.5 per cent, lymphocytes 17.5 per cent, and large mononuclears 2 per cent. The patient continued to have a fever of about 101° F. for a week, while at the same time he developed attacks of extreme epigastric pains and tenderness, and was relieved only after catharsis and the use of sedatives. Another blood count on October 28, when the patient's temperature was normal, showed P. M. N.'s 47.5 per cent, P. M. E.'s 21.5 per cent, lymphocytes 29 per cent and large mononuclears 2 per cent.

The patient continued to complain of extreme weakness and muscle pain for another two weeks, and then gradually made a recovery.

SKIN TESTS

On November 11 a series of skin and precipitin tests was done on these cases. The antigen (Bachman's) was obtained through the courtesy of Dr. Benjamin Schwartz of the U. S. Department of Agriculture.

In the markedly positive cases a wheal presented itself at the site of intracutaneous injection within 10 to 15 minutes. This was raised, about three-eighths to one-half inch in diameter, and showed the presence of pseudopods. There was surrounding inflammation about this raised area which was red and angry looking. This reaction persisted sometimes for 24 hours. Coca's solution (sodium chloride 0.7 per cent, sodium bicarbonate 0.05 per cent, phenol 0.4 per cent) was used as a control. Bachman's antigen in Coca's solution was used in dilutions of 1-100, 1-1000 and 1-10,000 (Figure 2).

It may be noted from the foregoing results that skin tests were markedly positive in the first seven cases listed, and definitely positive in the eighth case. In regard to the control tests done on non-trichinosis cases negative results were obtained in all cases except one (R. K.) which gave positive reactions in all dilutions and also was markedly positive to Coca's solution. This patient was possibly phenol sensitive. It is to be noted also that two patients who had markedly positive Wassermann tests did not react to the Bachman antigen.

PRECIPITIN TESTS

Precipitin tests were also done according to the method of Dr. George W. Bachman using his antigen in Coca's solution and floating it in various dilutions above the serum to be tested.

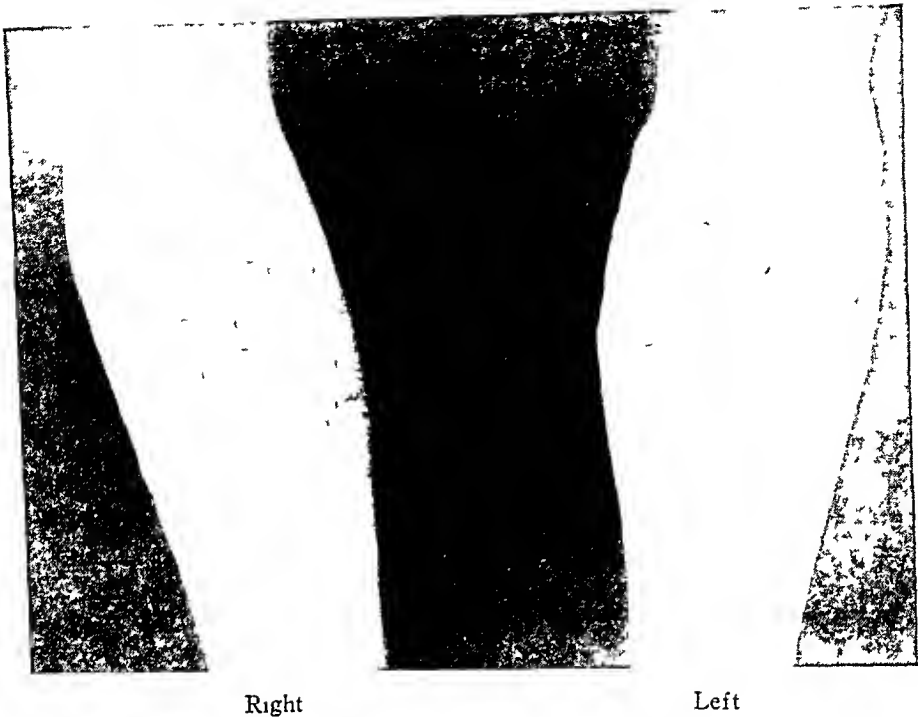


FIG 2 Right forearm showing positive reactions, reading from above downward in 1-100, 1-1000, and 1-10,000 dilution of antigen Left-arm Coca's solution, no reaction Test done on patient P K (Photo from painting in watercolor)

RESULTS OF SKIN TESTS ON PATIENTS

| Patient | Diagnosis | Estimated Day of Illness | 1-100 | 1-1000 | 1-10,000 | Coca's Solution |
|---------|-----------|--------------------------|-------|--------|----------|-----------------|
| J W | trich | 47 | ++++ | ++++ | ++++ | - |
| M B | trich | 47 | ++++ | ++++ | ++++ | - |
| G S | trich | 44 | ++++ | ++++ | ++++ | - |
| H L | trich | 44 | ++++ | ++++ | ++++ | - |
| G H | trich | 42 | ++++ | ++++ | ++++ | - |
| P K | trich | 32 | ++++ | ++++ | ++++ | - |
| M K | trich | 32 | ++++ | ++++ | ++++ | - |
| F M | trich | 27 | ++ | ++ | ++ | - |

Control Tests on Non-Trichinous Cases

| | | | | | | |
|-------|-------------|--|------|------|------|------|
| C K | diabetes | | - | - | - | - |
| J S | cardiac | | - | - | - | - |
| M K K | cardiac | | - | - | - | - |
| L J | lues | | - | - | - | - |
| R K | chr mastoid | | ++++ | ++++ | ++++ | ++++ |
| F deO | lues | | - | - | - | - |

It is evident from these tabulated results that the precipitin test in trichinous patients does not yield as definitely positive results as does the skin test

As stated above, the use of these tests began in 1928, when George W

RESULTS OF PRECIPITIN TESTS ON PATIENTS

| Pt | Diag | Day | 1-100 | 1-500 | 1-1000 | 1-2000 | 1-5000 | 1-10,000 | Coca's Solution |
|-----|-------|-----|----------|-------|--------|--------|--------|----------|-----------------|
| J W | trich | 47 | not done | | | | | | |
| M B | trich | 47 | + | + | - | - | | | - |
| G S | trich | 44 | | \pm | - | - | | | - |
| H L | trich | 44 | - | | - | - | | | - |
| G H | trich | 42 | + | + | - | - | | | - |
| P K | trich | 32 | | + | | - | - | - | - |
| M K | trich | 32 | + | - | - | - | | | - |
| F M | trich | 27 | - | - | - | - | | | - |

Control Tests on Non Trichinous Cases

| | | | | | | | | |
|-------|--------------|---|---|---|---|--|--|---|
| J S | cardiac | - | - | - | - | | | - |
| M K K | cardiac | - | - | - | - | | | - |
| L G | urticaria | - | - | - | - | | | - |
| R K | chr mastoids | - | - | - | - | | | - |
| F deO | lues | - | - | - | - | | | - |

Bachman was able to produce a satisfactory antigen of the *Trichinella spiralis* for precipitin tests, and showed the appearance of precipitins after the thirtieth day in experimental infection with rabbits. He also demonstrated precipitins in the serum of man infected with *Trichinella spiralis*.

Again in 1928 he showed the presence of a local skin reaction specific in character following the intracutaneous injection of *Trichinella spiralis* protein. These skin reactions appeared as early as the second day after feeding trichinous meat experimentally to rabbits. Again in 1928 he confirmed the previous work in regard to skin tests using 1-100 dilutions and showed the presence of precipitins experimentally 20 to 30 days after infection. He therefore advised the use of skin tests rather than precipitin tests, as the skin test was easier to do and appeared much earlier. In 1928 Bachman simplified his precipitin test using Coca's solution with his antigen instead of a neutralized antigen of definite H \pm ion concentration. He also regarded the antigen in Coca's solution as more potent, precipitins being detected some five to 20 days after infection. In a study of complement fixation in experimental trichinosis Bachman and Menendez demonstrated the presence of antibody formation in rabbits 25 days after infection.

In 1929 Stoll reported the application of the precipitin test in three cases of human trichinosis. Bachman obtained positive reactions in all three cases in high dilutions.

Hunter in 1931 demonstrated precipitins in three cases of human trichinosis with indefinite or negative results in three other suspected cases. Swinertord and Waddell used skin tests in five cases of trichiniasis and obtained positive reactions.

Augustine and Theiler in 1932 found the precipitin test to be reliable in detecting trichinosis in swine and to be highly specific. They also found that although trichinosis in man was invariably detected by the precipitin

test, the diagnostic value of the test was diminished by the fact that it was also positive with individuals who had recently taken quinine. They regarded the intradermal test as specific for trichinosis in man and swine in high dilutions up to 1-10,000 and higher. They also found precipitin and intradermal tests more accurate than muscle examination in the swine.

In 1933 McCoy, Miller and Friedlander tested a series of 88 persons who were said to have had trichinosis with skin tests. They obtained immediate positive reactions in 92 per cent of cases within two to six weeks after infection. From that time on, the greater the period that elapsed between infection and skin test, the less the number of positives. In persons ill three and one-half to seven and one-half years prior to the tests, only 62 per cent were positive. They also did control tests on 104 persons and showed an incidence of only 4 to 6.5 per cent positive. They also showed that persons infected with *Trichuris trichiura* gave 18 per cent of positives in 1-10,000 dilutions and 62 per cent positives in 1-500 dilutions. They regarded the latter reactions as a group reaction of a related parasite.

DISCUSSION

In a review of 137 cases reported in the literature since 1928, in which the reference is made to the source of infestation, I find that in only 22 cases was the cause given as uncooked pork. Of these 22 cases 13 ate pork bologna or smoked ham and only 9 ate raw pork or raw sausage. So that while no brief is held for raw pork, it must be stated that most of the cases of trichinosis that did occur were due to improperly cooked pork.

In view of the fact that no specific therapeutic agent has as yet been found, in spite of repeated attempts at intravenous medication, the treatment must still be symptomatic. The encystment of the parasite by the connective tissue and calcium results in a regression of symptoms. Calcium could therefore be given after the first week or 10 days. Marked lowering of the blood pressure is a feature of severe trichinosis, and in such cases vasomotor stimulation is of course indicated.

McCoy in 1931 showed that rats developed immunity to *Trichinella spiralis* and that they were able to withstand more than twice the lethal dose of larvae. This immunity was a comparative rather than a total immunity. In 1932, in studying the length of adult life of *Trichinella spiralis* in rats, he showed that the dose of infection influenced the length of time the adult worms persisted in the intestine. There are however, two factors to be considered. One is resistance to the exotoxin and the other is the resistance to the migration of the organism itself. While there is hope of producing a serum capable of an antibody response to the exotoxin, the migration of the larvae through the blood and tissues will probably have to be controlled by chemical agents.

Miller, McCoy and Bradford in 1932 questioned the therapeutic value of arsphenamine derivatives and antimony and potassium tartrate in the treatment of human trichinosis. They also tried out a host of other therapeutic agents with no beneficial result.

It has been found that trichuris, a related organism to trichinella which gives group reactions in concentrated dilutions to trichinosis antigen, is readily affected by oil of chenopodium in the intestinal tract. I have therefore used oil of chenopodium in the early stages after initial purging. I have also given calcium gluconate by mouth after the first week following the onset of symptoms, and adrenalin as indicated, especially where there is marked edema of the face and eyelids.

In the past, physicians have been perhaps hesitant in reporting possible cases of trichinosis, especially in the rural districts as they have had little access to pathological laboratories where muscle sections could be studied. At the same time others have hesitated due to the difficulty in obtaining permission for biopsy. With the use of the new intracutaneous test of Bachman many more cases will probably be reported, as the diagnosis may be made much more accurately.

The intracutaneous test is easier of application and more definite in its results. It is also obtained earlier. However, it has the one drawback that repeated tests sensitize the individual to the antigen so that subsequent tests become positive even in normal persons. If a negative skin test is obtained a subsequent positive one would be doubtful. The main recourse would then lie in the precipitin test and the further refinement in the ease of application of this test is to be looked forward to.

In any discussion of this disease, its prevention must be considered. The best prophylaxis is the thorough cooking of pork. There is no inspection by the Department of Agriculture, with a view of detecting the trichinae. It has been found that in Germany of 6329 cases of trichinosis with 318 deaths, 2042 cases and 112 deaths were from meat that had been examined and released for trade as free of trichinae. The inspection must be microscopic, and cases are frequently missed in spite of elaborate systems of inspection. (Tice)

Pork products usually eaten without cooking are processed under the following regulations when they originate in establishments under federal supervision. They are so cooked that all parts of the products attain a temperature of not less than 137° F (59° C) or refrigerated for a period of not less than 20 days at a temperature of not higher than 5° F (minus 15° C) or prepared with special curing methods of known effectiveness in killing trichinae. Augustine in 1933 has demonstrated that raw pork in commercial communities may be rendered safe as far as trichinosis is concerned by either rapidly lowering its temperature to minus 35° C or by rapidly lowering its temperature to minus 18° C and maintaining that point for at least 24 hours. As to the possibility of using the intracutaneous test for trichinosis on hogs, in spite of its efficiency it is doubtful whether this method of prophylaxis will prove practical.

CONCLUSIONS

- 1 Eight cases of trichinosis are reported with recovery
- 2 In all cases infestation occurred from cooked pork or sausage

3 Edema of the eyelids, intense headache and pain on flexing or extending the neck were outstanding features of all cases

4 Skin tests were positive in all cases in 1-100, 1-1000, and 1-10,000 dilutions. Precipitin tests were also done with less positive results

5 Mild trichinosis may be very easily overlooked or mistaken for grippe or other infectious diseases

6 Trichinosis may be found in scattered cases as well as in large groups

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PAROXYSMAL AURICULAR FLUTTER WITH 1 1 AURICULO-VENTRICULAR RATIO⁴

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INTRODUCTION

AURICULAR flutter with a ventricular rate of 70 to 160 a minute is a common condition and is met with, according to McMillan and Bellet,¹ once in every 80 cases of heart disease or of suspected heart disease, but auricular flutter with ventricular rates above 200 are quite rare. The rate of auricular contractions in flutter ranges from 220 to 400² or over, in untreated cases, while the ventricular response is usually slower. The auriculo-ventricular ratio is 2 1, 3 1, or 4 1, rarely it may be 6 1 or 8 1 as in cases of complete block³. At times the ventricular response is irregular. Very rarely, the refractory period of the A-V node suddenly decreases and the junctional tissue becomes extremely sensitive to the auricular stimuli, transmitting all of them to the ventricle. In such instances an extremely rapid heart rate follows.

Such changes in the refractory state of the A-V node and in the irritability of the junctional tissue take place in auricular paroxysmal tachycardia, where ventricular rates as high as 250 have been reported⁴. Rarely such phenomena occur in auricular fibrillation, although here not all the auricular stimuli are transmitted by the junctional tissue. Nevertheless ventricular rates of 220 have been reported⁴. A similar condition with rapid transmissions of impulses by conducting tissue, though perhaps in the opposite direction, occurs in paroxysmal ventricular tachycardia where rates of 200 to 300 have been recorded⁵⁻⁸. The best example of this mechanism is observed in auricular flutter with an established 2 1 auriculo-ventricular ratio, where suddenly the refractory period of the A-V node becomes shorter than the auricular cycle. A sudden doubling of the ventricular rate follows and a 1 1 rhythm or a 1 1 auriculo-ventricular ratio, is established. In some cases however, the auricular flutter and the 1 1 ventricular response begin simultaneously in a paroxysmal attack.

Theoretically, heart rates between 200 and 400 may be expected when the ventricle takes up the rate of the fluttering auricle. It seems, however, that the junctional tissue cannot transmit stimuli faster than about 300 per minute, for these are the highest rates recorded in the human heart^{8,9}. According to Lewis,¹⁰ this is not only because the junctional tissue is unable to transmit impulses at such a fast rate but also because stimuli coming so fast are poorly conducted. Thus in auricular rates above 300 to 350 a 2 1 block is established. When the auricular rate drops below 300, conduction

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improves, and if the junctional tissue is sensitive enough to transmit all stimuli, the ventricular rate is the same as the auricular rate and a 1:1 rhythm ensues.

The usual heart rates in auricular flutter with 1:1 ventricular response are 220 to 300. Blackford and Willis⁹ reported a rate of 320 in one case, but this was estimated by counting through a stethoscope, the electrocardiographic rate of the same patient was 300 or slightly over. Such rapid rates last from several minutes to several hours, and very rarely for several days. Alarming symptoms are usually ushered in, such as palpitation, precordial pain, pulmonary edema, and syncope. In rare instances, death may ensue, as in the case reported by Bourne,¹¹ where a rate of 260 lasting seven days in a woman of 28, ended fatally from coronary occlusion by an embolus from an antemortem clot in the left auricle.

A similar case is here reported, though in this instance the patient recovered from the attack.

CASE REPORT

An American seaman, a radio officer, age 48 years, was admitted to the U. S. Marine Hospital Ellis Island, April 20, 1933. His chief complaint was shortness of breath and palpitation. The family history was unimportant. Habits were moderate. There was no history of childhood diseases, no rheumatic fever or chorea. The patient denied luetic infection.

For the past 10 to 15 years he had been having periodic attacks of palpitation, and for the last four years he had noticed that he had shortness of breath on exertion and that the attacks of palpitation were becoming longer, lasting about a half hour and recurring more frequently. However, he was never much handicapped by these symptoms. Three weeks before admission to the hospital, after returning to his ship from a mountain climbing trip, while the ship was in port, he was seized with severe palpitation followed by shortness of breath and a constriction of his chest, the like of which he had never experienced before. He was in great distress but had no characteristic precordial pain. By the time the ship surgeon was able to see him he had improved somewhat but began to bring up frothy, pink sputum. He was given injections and was ordered to stay in bed. Shortness of breath continued and a week later, while in bed, he developed another attack of palpitation associated with cough, and pink frothy sputum. This attack was not as severe as the preceding one. Improvement followed and the patient came to the hospital two weeks later, that is, three weeks after the first attack.

On admission he brought a note from the ship surgeon stating that the patient had had two attacks of pulmonary edema and that during these attacks the pulse was 120 to 130. He had responded well to hypodermic medication of morphine and atropine, and intravenous digitalis. The pulse had dropped below 90 each time following the medication. In the period of 10 days he had been given digitalis equal to three-fourths of the estimated dose required for digitalization, and as the patient improved the drug had been discontinued.

On examination in the hospital the patient appeared well developed and well nourished and did not look ill, except for moderate dyspnea. The general examination was negative except for poor condition of the teeth and for a small inguinal hernia. The heart was slightly enlarged to the left, the sounds were distinct, there was no gallop rhythm and there were no murmurs. The rate was 76 and the rhythm was regular. The lungs were clear, the liver was not enlarged and there was no edema of the ankles. There was no evidence of peripheral arteriosclerosis. The blood pres-

sure was 144 systolic and 90 diastolic, and the temperature 37°C . The urine showed a faint trace of albumin and rarely a hyaline cast. Hemoglobin was 80 per cent, red cells were 4,400,000 and white cells 8,000 per cu mm. The differential count was normal. The blood Wassermann was negative. Roentgen-ray film and fluoroscopic examination of the heart showed it to be moderately enlarged to the right as well as to the left. The retrocardiac space was normal. The electrocardiogram showed left axis deviation, slight elevation with modified cove planing of the (S-T)₁ segment, faint elevation of (S-T)₂ and (S-T)₃, and P₂ was diphasic. The chest lead (the right electrode posteriorly and the left electrode anteriorly) showed distinct elevation of the (S-T) segment. The rate was 84. (See figure 1.)

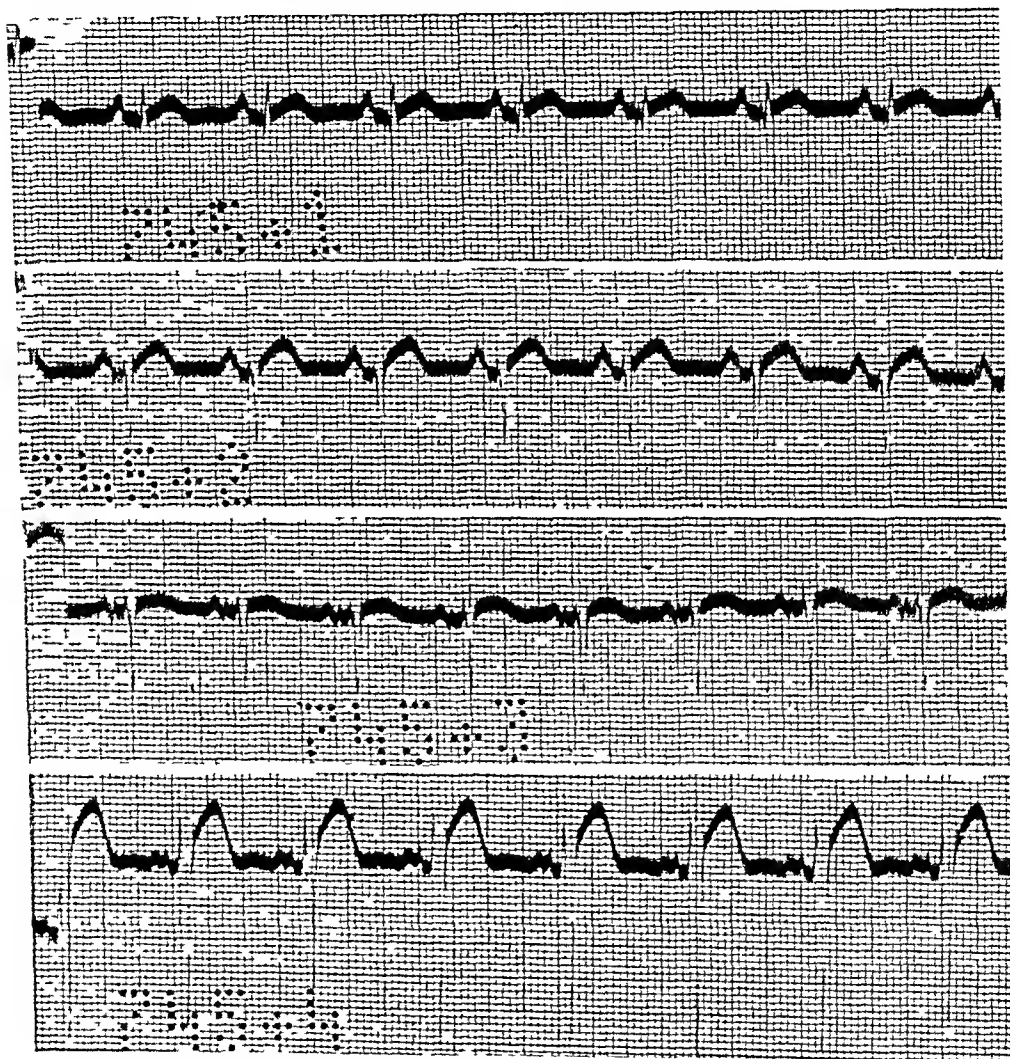


FIG 1 Electrocardiogram taken on the day of admission showed elevation with modified cove planing of the (S-T)₁ segment, faint elevation of (S-T)₂ and (S-T)₃, and P₂ was diphasic. There was left axis deviation. The chest lead taken with the right electrode posteriorly and the left electrode anteriorly showed distinct elevation of the (S-T) segment. The rate was 84.

The admission diagnosis was Paroxysmal tachycardia with pulmonary edema and recent myocardial damage due to coronary occlusion. The patient was put on

mild sedatives and allowed to be semi-ambulatory. Two weeks after admission he stated that his palpitation began to reappear, usually at night, lasting 15 to 30 minutes. On two occasions he had pain in the region of his heart. His pulse rate during the palpitation was recorded by the night nurse as 120. Electrocardiographic tracings showed no change except slight flattening of T_2 and pointing of T_1 and T_3 . He was given digitalis by mouth with the hope of reducing the frequency of his palpitation. He received 35 grams in 17 days. During this time he was doing very well, had no precordial pain or palpitation. The heart findings were about the same as on admission, except that at times a systolic murmur was heard at the base. Electrocardiogram showed no digitalis effect. On June 5, in the afternoon, he suddenly developed severe palpitation associated with pallor, cold perspiration, and moderate dyspnea. The heart rate was very rapid and could not be correctly estimated. It was approximately 250 a minute and regular. Vagal pressure as well as pressure on the eyeballs at this time had no effect. He was given a hypodermic injection of morphine, an ice bag to his precordium, and was put to bed. (See figure 2.)

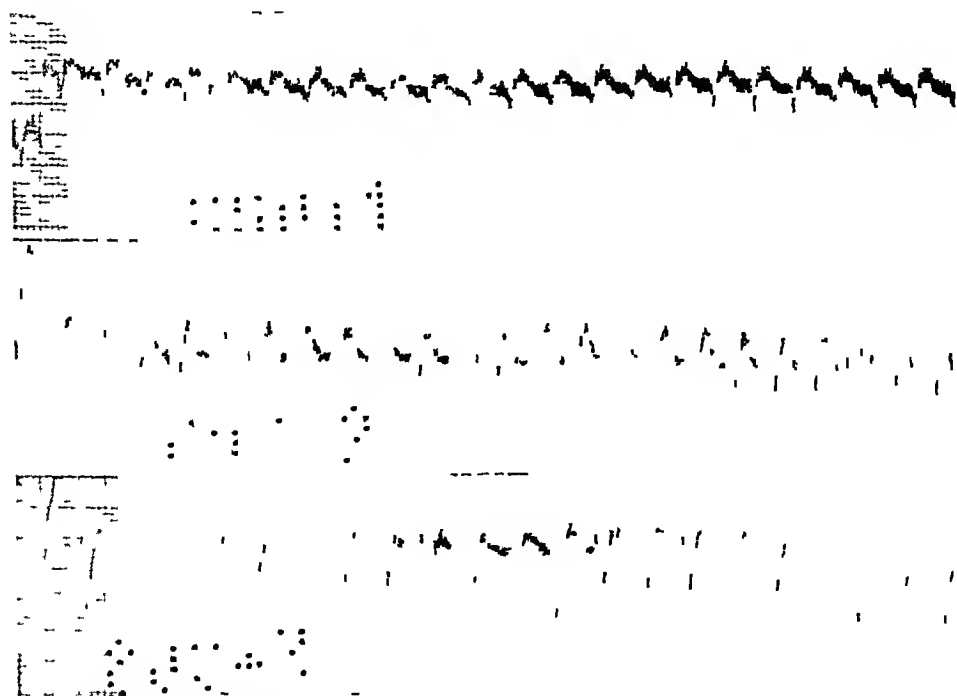


FIG. 2. Electrocardiogram taken about a half hour after onset of tachycardia showed a rate of 240 with a regular rhythm. The appearance of the complexes suggested auricular flutter with a 1:1 auriculo-ventricular ratio.

Electrocardiographic tracings taken during this paroxysm of rapid heart action showed a rate of 240 with a regular rhythm. The appearance of the complexes suggested auricular flutter with a 1:1 auriculo-ventricular ratio. This rate continued for about two hours, after which it was recorded by the nurse as 120. Unfortunately, an electrocardiogram was not taken during this halved rate. A tracing on the following morning showed a rate of 76, with complexes essentially the same as had been recorded before the onset of his rapid rate. Physical examination of the heart revealed no change and the patient was free from symptoms. He remained in the hospital for another week without recurrent attacks of tachycardia, and left for home while he was still moderately dyspneic on exertion.

About eight months later the patient reported by mail that he had not been able to return to work. His attacks of palpitation and shortness of breath were likely to occur on the slightest exertion. He had many attacks of the "milder type" and "two of the extremely rapid heart fluttering type with pink sputum." On several occasions he was able "to ward off an attack of the extremely rapid type by bending forward when the heart seemed undecided whether to go back on its regular beating or to take up the very fast palpitating route."

COMMENT

Although no electrocardiographic tracing has been obtained of the patient prior to admission, it is reasonable to assume that the "mild attacks" of palpitation with rates of 120 to 130 (half that of the subsequent 1:1 rhythm) were attacks of paroxysmal auricular flutter with a 2:1 auriculo-ventricular ratio. Since it is sometimes difficult to differentiate electrocardiographically between paroxysmal tachycardia of very high rate and regular rhythm, and that of paroxysmal auricular flutter with a 1:1 ratio as in the case of Bunn,⁸ the mild attacks of this patient with a rate exactly one-half of the one recorded during his hospital stay, help in a measure and lead to the diagnosis of previous paroxysms of auricular flutter. The electrocardiographic findings during the normal rate, the history of a sudden onset of severe shortness of breath with constriction of the chest, which occasioned admission to the hospital, and the subsequent dyspnea and disability strongly suggest a coronary occlusion and occurrence of pulmonary edema, during the paroxysm of tachycardia. As stated above, only one case was found in the literature where a coronary occlusion occurred during a prolonged attack of auricular flutter in a case of 1:1 rhythm. It is supposed that this case is of similar nature with probably a less extensive occlusion. This case also adds one more to the small group where a 1:1 rhythm developed not during established flutter of 2:1 block as is usual, but as a paroxysm of 1:1 in a heart with normal rate and rhythm subject to paroxysms of 2:1.

The literature records only 29 instances of auricular flutter with 1:1 ventricular response, testifying to the comparative rarity of this condition. Eighteen of these were gathered from the literature by Parkinson and Bedford¹² in 1927. Bedell¹³ in 1933 carefully analyzed 21 recorded cases, and added three to the list.

The incidence of 1:1 rhythm in auricular flutter is given by Bedell as 4 per cent of all flutter cases, while McMillan and Bellet¹ met with only two instances among 80 cases of auricular flutter.

The condition is paroxysmal and develops usually in cases of established flutter of 2:1 auriculo-ventricular ratio^{1, 9, 12, 14-22} and others. Bedell seems to reject those cases where only paroxysms of 1:1 rhythm were recorded, without previous evidence of established flutter. Since auricular flutter is not considered as established unless it continues for more than two weeks,^{1, 12} a paroxysm of 1:1 ratio may very well develop during such an interval. Such instances are seen in the cases of White and Stevens,²³ Allan,²⁴ Parkin-

son and Mathias,²⁵ Bourne,¹¹ and in the case included herewith. Moreover the paroxysm of 1:1 ventricular response may arise in cases of auricular flutter even with 4:1 block as was clearly shown by Winterberg.¹⁶

The age limits of the reported cases are between 19 and 52. There are five instances in children below the age of 6, Koplik,²⁶ Poynton and Wyllie,²⁷ Lewis,²⁸ and Sachs.²⁹ According to Wilson,³⁰ however, it is difficult to distinguish auricular flutter of 1:1 auriculo-ventricular ratio in children from paroxysmal tachycardia of auricular origin. He classes these conditions as tachysystole. Bedell¹³ thinks that in older individuals the junctional tissue cannot transmit stimuli as rapidly as in younger and middle-aged people, hence the rarity of 1:1 rhythm in individuals above 50.

Out of 29 cases gathered from the literature, 15 had no evidence of heart lesions. In six instances the authors did not state whether or not there was evidence of heart disease. The remainder of the cases were associated with rheumatic heart disease, hypertension, arteriosclerosis, hyperthyroidism, cardiovascular lues, and congenital heart disease. It is significant that whereas in established flutter the heart is damaged in about 90 per cent of the cases, and only one out of 65 was free from serious cardiac damage in McMillan and Bellet's series,¹ in paroxysmal 1:1 rhythm 50 per cent or over are free from cardiac lesions.

The ventricular rates in the reported cases ranged between 222 and 300. The onset of the paroxysm usually follows exertion and rarely may follow quinine medication, as mentioned by Bedell with reference to Parkinson and Bedford's cases.¹² The duration of the attack varies from minutes to hours, and the symptoms vary with the ventricular rate. They are usually severe and may cause syncope, pulmonary edema, myocardial failure, and coronary embolism. However, two patients of Parkinson and Bedford and one of Blackford and Willis,⁹ with heart rates of 254, 275, and 320, respectively, were able to be up and about for several hours without apparent distress. The effect of vagal pressure varies, more frequently it is of no help.

There are four deaths on record among 29 cases, only one definitely attributable to the tachycardia—the case of Bourne with the coronary occlusion. Of the two deaths in the series of Blackford and Willis, one had no electrocardiographic evidence of 1:1 rhythm, and the diagnosis in the other case was equally uncertain. The heart rate in Bedell's case was not known before death. The prognosis is guarded because the paroxysms tend to recur in greater frequency.

Auricular flutter with 1:1 ventricular response must be differentiated from the paroxysmal tachycardias of auricular as well as of ventricular origin. In the tachycardias the A-V ratios are naturally always 1:1, although in rare instances as stated by White,² a temporary auriculo-ventricular or intraventricular block may develop. However, their rates are usually below 200, and the complexes on the electrocardiogram are not entirely uniform and regular. Furthermore they are usually initiated by an

extrasystole In flutter with 1 1 response, however, the established A-V ratio prior to the paroxysm usually is 2 1 The ventricular rate is usually above 200 and frequently above 250

SUMMARY

A case of paroxysmal auricular flutter with 1 1 auriculo-ventricular ratio is presented, where a coronary occlusion and pulmonary edema are believed to have occurred during a previous paroxysm The literature is reviewed of all the presumably recorded cases and the incidence of the condition, and the associated heart rates, symptoms and cardiac lesions are discussed

The writer is indebted to Dr Irving R. Roth, Consultant Cardiologist to the U. S. Public Health Service, for his help in preparing this paper

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DERMATOMYOSITIS*

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Dermatomyositis was described by Steiner¹ as "an acute, subacute or chronic disease of unknown origin, characterized by gradual onset with vague and indefinite prodromata followed by edema, dermatitis and multiple muscle inflammation." If this description be amended to read "multiple non-suppurative muscle inflammation," it becomes definitive. Although the disease was recorded independently by E Wagner,² Unverricht³ and Hepp⁴ in 1887, Steiner was able to collect only 28 undoubted cases in 1905. Since then some 75 additional instances have been noted, practically all in the English, German and American literature. Excellent reviews are those of Rosenthal and Hoffman⁵ and Wheeler and Harbin⁶. Since the disorder may be acute, subacute or chronic, there is much variation in the details of symptomatology and pathology. Exact diagnosis is made more difficult by the many points of similarity which exist between chronic dermatomyositis, generalized scleroderma, calcinosis and myositis fibrosa and by the fact that mixed cases have been observed.^{7,8} Langmead⁹ has made an interesting comparative analysis of the four conditions, and advances the theory that they are different and possibly sequential manifestations of a single morbid process. Certainly all gradations seem to exist between chronic dermatomyositis and generalized scleroderma.

ETIOLOGY

The etiology is quite indefinite. There is neither race nor sex predilection, and children are affected less often than adults. The disease seems to occur more frequently during the winter. Many cases have followed some type of acute infection, particularly of the upper respiratory tract. Some have occurred after gastrointestinal disturbances probably of toxic origin, while others have developed after severe exposure to cold. Numerous instances have appeared *de novo* in previously healthy individuals. Unverricht³ thought that it might be due to infection with Gregarines on account of the similarity of the histological picture in dermatomyositis to that in canine gregarinosis. Recently an analogous suggestion was made by Theobald Smith,¹⁰ who noted the similarity of the pathological findings to those in sarcosporidiosis of swine. Staphylococci and streptococci occasionally have been isolated from the muscles and from heart's blood obtained at necropsy. It seems likely that the syndrome may result from various infections and intoxications. The only group of cases suggesting contagion

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which has been observed, was reported by Sick¹¹ as occurring among the nurses at the Tubingen Psychiatric Clinic. Later observers have questioned the diagnosis in this group.

SYMPTOMS

The onset may be acute with malaise and fatigue followed by muscle pains, local swelling and rigidity and fever. More often there is a prodromal period of one to three weeks during which the complaints include fatigue, vague rheumatoid pains, insomnia, anorexia and sometimes gastrointestinal disturbances. Pain begins more often in the legs and is followed by weakness and swelling. In the early stages the consistence of the muscles may be soft and doughy, but with the progress of the disease induration becomes more marked until in cases of long standing the affected musculature is hard and lumpy, with contractures and great limitation of movement. Muscular involvement is usually bilaterally symmetrical but may be limited to a single limb. The legs and arms are most frequently attacked, the flexor muscles more than the extensors, although the buttocks, abdomen, neck and face are often implicated. Less frequently myositis extends to the diaphragm, intercostal muscles, pharynx, tongue and external muscles of the eyes. Only rarely is there evidence of myocarditis. The tendon jerks are diminished but a reaction of degeneration is found in only the most chronic cases.

Edema appears early, as a rule with the onset of fever. It is most marked over the face and the involved muscles, it is brawny, seldom pits on pressure, is often bilaterally symmetrical and may attain striking proportions. The hands and feet are said never to swell. During the first few days of illness the skin even where no edema is present may be smooth and glistening. The eruption is multiform and may be erythematous, scarlatina-form, erysipeloid or urticarial. Some cases show lesions resembling erythema multiforme and erythema nodosum. Desquamation and pigmentation may follow the rash. At times the buccal or pharyngeal mucosa may be involved with production of ulcerative stomatitis or angina.

In the more severe and chronic cases, edema and muscle swelling are persistent with great loss of strength and development of contractures. Paresthesias may be troublesome and hyperhidrosis of the affected skin is frequent. Fever of variable degree and duration is the rule though afebrile cases have been described. The temperature is said never to exceed 104° F. The spleen has been enlarged in many instances, and is always described as very soft. The blood shows little of diagnostic value. Marked leukocytosis is exceptional and there is no constant change in the differential formula, although Wermer¹² reported a case in which eosinophilia of 38 per cent was present and McGarrahan¹³ saw a patient whose eosinophiles rose to 29 per cent. There are no constant urinary findings. The basal metabolic rate has shown no significant modification.

PATHOLOGY

Changes found in the skin and muscles vary with the duration and severity of the disease. Grossly the muscles are pale red to yellow and may show yellowish-grey or diffuse reddish streaks. They are often moist and friable although the consistence may vary from boggy to almost ligneous. In early cases the microscopic picture is that of a parenchymatous and interstitial myositis, the fibers separated by edema and showing all stages of degeneration from finely and coarsely granular to hyaline, waxy or fatty change. Fragmentation is found and is perhaps the first evidence of degeneration. It is characteristic that the process is most irregular. Normal fibers are found among diseased ones or small areas of degeneration occur in apparently normal muscle. There are conspicuous interstitial perivascular accumulations of polymorphonuclear and lymphocytic cells. The walls of the blood vessels may appear thickened with the absence of any demonstrable proliferation of the vascular coats. In advanced cases there is much increase in connective tissue, the perimysium and endomysium being equally involved. Evidences of muscle regeneration are present and occasional normal muscle fibers may be seen in the midst of areas of newly formed connective tissue. In other instances the arterioles show intimal proliferation and hyaline degeneration, sometimes with occlusion. In the skin there is irregularity in the thickness and in the architecture of the epidermis with distortion of the papillae, and occasional hyperkeratotic follicles. The dermis shows edema and perivascular infiltration with round cells. The panniculus may be atrophic with hyaline degeneration of the collagen and cellular infiltration of the fat lobules. Deposits of calcium have been noted in three instances. There are no specific pathologic changes in the viscera.

DIAGNOSIS

During the acute stage dermatomyositis may so simulate trichinosis that several of the early case reports used the title "Pseudotrichiniasis." Fever and constitutional reaction are more severe and prolonged in trichinosis, the edema is softer, and swelling of the face and eyelids is apt to be more striking. Involvement of the extraocular muscles and of the musculature of the jaws and pharynx is more common. Skin changes aside from edema are neither prominent nor progressive. Leukocytosis and eosinophilia are not commonly features of dermatomyositis. Absence of a history of gastrointestinal disorder, failure to find larvae of trichinella in the stools and finally histological examination of a bit of muscle are most important in differentiation.

Scleroderma must be excluded in the more chronic cases. The absence of myositis is perhaps the only adequate criterion as the tendency is to classify all instances of sclerodermatous change in the skin associated with muscle infiltration as dermatomyositis. At times differentiation may be impossible.

Syphilitic myositis and various types of suppurative myositis may present problems of differentiation as also may polyneuritis and trophic neuroses. In none of these is the triad of eruption, edema and myositis present.

PROGNOSIS

Approximately 50 per cent of the reported cases have ended fatally, some in as short a time as three weeks, and others after months. Death has resulted from respiratory failure or, more properly, suffocation when there was extensive disease of the respiratory muscles. Bronchopneumonia is the usual cause of death, frequently an aspiration pneumonia secondary to myositis of the pharynx. Heart failure the result of myocarditis has apparently been fatal in a few instances. Prognosis therefore is grave in all cases with extensive involvement of the muscles of deglutition and respiration, but in others it may be considered good. The disease may run an acute course with recovery or may progress from one group of muscles to another producing invalidism for as long as two years. Complete recovery has occurred after extensive contractures have developed.

TREATMENT

All methods of therapy have been ineffectual in the great majority of instances. Salicylates, quinine, calcium chloride and arsphenamine have been credited with isolated cures.

CASE REPORT

H. B. (Unit No. 272), a white boy 14 years old, was admitted to the University Hospital December 16, 1932 complaining of generalized swelling and of soreness of the neck, jaw muscles, abdomen and back.

The family history was irrelevant, no other members of the family were ill. The past medical history included measles and chicken pox during infancy and frequent upper respiratory infections. Six days prior to admission there had been a superficial scalp wound which caused moderate hemorrhage but no particular discomfort.

The present illness began five days previously with coryza, occipital headache and general aching which persisted until the day before admission when there were chilly sensations, fever, and swelling of the face and legs. During the night there was profuse sweating and the abdomen and back became quite painful. On the morning of admission, eating had been impossible on account of soreness of the jaws and neck muscles.

Examination showed a well nourished and developed boy apparently quite ill. The temperature was 103° F, the pulse 120, and the respirations 36. He lay supine by preference, active or passive movement causing pain in the neck, back and abdomen. There was brown, non-pitting edema of the face and eyelids, of the legs and to a slight degree of the trunk. The skin over these areas was smooth and shiny. The face and upper thorax presented a diffuse, dusky red erythema which blanched on pressure, there was slight, much paler redness of the legs below the knees. The muscles of the neck, lumbar region, abdomen and legs were firm and quite tender on pressure.

The head was of normal conformation, the hair abundant and of good texture. There was a healing scalp wound over the right temporo-parietal region which presented no evidence of infection. The ears were negative. The eyelids were moderately edematous and the palpebral conjunctivae deeply injected. The left eye showed marked internal strabismus with limitation of outward rotation, ocular movements otherwise were well performed and not painful. The pupils were round, equal and reacted to light and accommodation. Ophthalmoscopic examination after dilation of the pupils showed nothing remarkable. There was no tenderness over the paranasal sinuses, there was a slight mucoid nasal discharge. The teeth were well preserved. The tongue was coated and a little tremulous. The tonsils were moderately large, red, free from exudate. The entire pharynx was diffusely reddened.

The neck looked normal, there was pain on movement but no rigidity. The thyroid was normal. The anterior cervical, epitrochlear and inguinal lymph nodes were large, soft, insensitive. The thorax was symmetrical and moved well. The lungs were negative throughout. The heart was normal in size and position, no thrills or shocks were noted. The first heart sound was of poor quality at all valve areas and systolic murmurs were heard at the mitral and pulmonic. There was no accentuation of the pulmonic second sound. The heart rate was 120, the rhythm normal, blood pressure 100 systolic, 70 diastolic. The abdomen was flat and showed general limitation of respiratory movement. The walls were held rigidly and there was general tenderness of the muscles. No other evidences of peritoneal irritation were noted. The liver, spleen and kidneys were not felt. The genitalia were normal. The extremities were negative except for the firm edema of the legs which extended from the ankles to the mid-thighs and the rigidity and tenderness of the underlying musculature. There was no evidence of arthritis. The superficial and deep reflexes were all present and seemed normally active.

Examination of the blood showed 5,000,000 erythrocytes and 17,000 leukocytes per cubic millimeter, hemoglobin 85 per cent. A smear showed no morphological abnormalities of the red cells, and no malarial parasites were seen. A differential leukocyte count showed 52 per cent polymorphonuclear neutrophils, 38 per cent eosinophils, 5 per cent lymphocytes, 5 per cent monocytes. The blood sugar was 98 mg per cent, the non-protein-nitrogen 26 mg per cent. The Wassermann and Kahn tests were negative. The urine contained a trace of albumin and a few granular casts. The phenolsulphonephthalein output was 45 per cent in one hour after intravenous injection. The stools were negative for cysts, ova and parasites, neither blood nor pus was present. The sputum showed no blood nor tubercle bacilli.

The admission diagnosis based on the presence of fever, edema, muscular soreness and eosinophilia was trichinosis. On account of the erythematous rash and red throat, mild scarlet fever was considered a possibility. The temperature fell rapidly, reaching normal on the second day and remaining normal after the third. The eruption faded on the second day leaving a faint brown stain. No desquamation occurred. Edema resolved more gradually persisting until the fifth day. The cardiac bruits were not noted after fever ended although the heart rate remained between 88 and 100 during the entire period of hospitalization. Moderate muscular soreness and stiffness were present for some three weeks and the muscles of the thighs and legs felt firm. No change could be detected in the muscles of the neck and trunk. During the third and fourth weeks of observation the skin of the legs became increasingly tough and inelastic with definite loss of mobility. Repeated examinations of the blood showed persistent leukocytosis and eosinophilia. (See table.) Frequent search of the stools failed to discover parasites of any sort.

On January 3, 1933 a fragment of the right gastrocnemius muscle was removed for histological examination. The wound which had been closed by deep and superficial suture showed infection on the fifth day. *Staphylococcus albus* was recovered

TABLE I

| Date | W B C | P M N | Eos | Lymph | Mon |
|--------|--------|-------|-----|-------|-----|
| Dec 16 | 17,000 | 52% | 38% | 5% | 5% |
| Dec 22 | 20,000 | 54% | 26% | 19% | 1% |
| Dec 26 | 21,000 | 30% | 60% | 10% | 0 |
| Jan 3 | 12,250 | 66% | 10% | 22% | 2% |
| Jan 19 | 12,800 | 47% | 40% | 12% | 1% |

from the pus, and final healing delayed until the fourteenth day. Microscopical examination of the excised muscle showed marked edema with irregularly distributed degeneration of the muscle fibers some of which were fragmented, others hyaline, still others in a state of granular degeneration. There were focal areas of lymphocytic and polymorphonuclear infiltration many of which were interstitial, while others were around the arterioles. There were few if any eosinophiles in these areas of infiltration and no giant cells. No evidence of proliferation of muscle or connective tissue was seen. The walls of some of the arterioles were unduly thick but without evidence of medial or intimal proliferation. No larvae of *Trichinella spiralis* were found. The histological diagnosis was acute to subacute non-suppurative myositis.

The patient was dismissed on January 20, 1933. At this time very little muscular soreness or tenderness remained. The skin of the legs was glossy, firm and inelastic. There was definite diminution in the size of the gastrocnemius muscles of both legs and these as well as the quadriceps and hamstring groups were much firmer than normal. No contractures were present and there was little loss of function. The knee and ankle jerks on both sides were diminished. The boy was seen again five months after dismissal. There was no pain nor tenderness of the leg muscles but slight atrophy of the gastrocnemii was evident. The muscles of the thighs and legs remained firmer than normal but function was excellent. The skin had resumed a normal appearance but remained inelastic and immobile.

The case is recorded as one of dermatomyositis with an acute and benign course which gives every evidence of early complete recovery. The clinical resemblance to trichinosis was at the onset remarkable. No cause was found for the extreme eosinophilia.

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CONGENITAL OSTEOSCLEROSIS (MARBLE BONE)

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SINCE Albers-Schonberg¹ first wrote about this rare and interesting condition in 1904, descriptions of it with reports of approximately 30 cases have appeared in the literature. The majority of them originated in Germany with a few from America, Switzerland, France and Italy. Since most of the diagnoses have been made by accident while looking for other conditions, it is probable that it is not so rare as has been believed. Lievre² reminds us that it is not likely that the condition would in reality be so largely limited to the German speaking countries and suggests that the diagnosis has doubtless often been missed because of confusion with such other conditions as osteopsathyrosis, rickets, osteomalacia and Recklinghausen's disease. It must be remembered that our knowledge of this disease has been acquired only since the development of the roentgen-ray.

No one has yet offered a satisfactory explanation of the causation of congenital osteosclerosis. Pehu, Policard and Dufourt³ point out its apparent preference for the Anglo-Saxon race. Kudrjawtzeva⁴ believes it is a mutation of the germ plasma which is inherited as a recessive characteristic and which manifests itself through inbreeding. A few cases have been reported in the offspring of blood relatives. Karshner⁵ feels that it is a primary dyscrasia of the mesenchyme resulting in abnormal and excessive bone formation. The frequently irregular distribution of the bone density leads Pirie⁶ to suggest that the condition is due to a widespread infection beginning at the epiphyseal line and later spreading to the whole medulla. Since the giving of excessive amounts of irradiated ergosterol has produced in animals a hypercalcification, similar in some ways to this condition, the suggestion has been made more than once that an improper vitamin balance might be responsible. It has not been possible to connect the condition with syphilis or any known pathologic condition of the endocrine glands. So, for the present, we must be content with the statement that it is a hereditary, familial and constitutional disease of unknown etiology which may begin in utero.

The pathology consists primarily of a disturbance of ossification consisting of an increase in the hard cortical bone to perhaps twice its normal thickness. The growth takes place from the endosteum entirely with a crowding of the marrow cavity, often with entire obliteration of this and of the spongiosa or with its replacement by fibrous tissue. The epiphyseal lines may show some irregularity with several transverse striations. Autopsy specimens of the bones are hard like ivory, but brittle, and may show old fractures. The marrow cavity may have disappeared. The upper ends of the humeri and lower ends of the femora show the greatest changes.

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Sometimes the sternum, ribs, scapulae and spinal column do not seem to be involved but the changes are usually more or less general including the short bones and those of the skull. Enlargement of the posterior clinoid processes seems to be particularly striking, and necrotic lesions of the alveolar border of the lower jaw have frequently been present. Schinz⁸ describes the microscopic picture thus: Cortex thickened, osteoblasts increased in every field, Haversian canals increased in number and ramifications, marrow spaces filled with fibrous tissue, Haversian canals and Howship's lacunae filled with numerous polynuclear osteoclasts. All these indicate an increased resorption of bone followed by a still more marked formation of it.

While the condition appears to be congenital, symptoms may not appear until later in life. Nearly all cases in young persons are underdeveloped physically. The long bones eventually attain their normal length if the individual lives, but the mature figure is generally slender and frail. Walking and talking are late in appearance and hydrocephalus with a retarded mentality is common. The type of facial expression is fairly characteristic. The features are broad, the eyes wide apart, the root of the nose sunken with the tip broad and turned up, the nares being round and far apart. The lips are thick and the hair abundant. The cranial bosses are prominent. Nystagmus is often seen and later optic atrophy and blindness due to the bony structures pressing upon the optic nerve as it passes through the foramen. The skin may be wrinkled and present a senile appearance. It seems that the bones utilize large amounts of calcium at the expense of the teeth, these are always late in eruption and tend to drop out or decay early. Suppuration and necrosis of the lower jaw has been the cause of death in several of the reported cases. Healing of the numerous fractures may be delayed resulting in deformities. These fractures occur from slight trauma, especially in older persons. Coxa vara, coxa valga, scoliosis, beaded ribs, deformed chests and epiphyseal enlargements are fairly common. An anemia, which varies in degree from mild to very severe, is common, and the blood picture sometimes simulates leukemia. The superficial lymph nodes are usually palpable, the liver is generally enlarged and the spleen is apt to be enormously enlarged and very hard.

The most outstanding characteristics are brought out by the roentgen-ray. The skeleton presents an almost uniform opacity, the bones transmitting no rays and appearing on the plate as structureless silhouettes. If seen at all, the medullary cavity is much reduced in size. The picture may look like one of incomplete exposure. The opacity may be more dense in the spine, pelvis, base of the cranium, upper femur and tibia. While the outlines of the bones are generally regular, local thickening may be observed especially along the upper humeri, the lower femora, the ribs, scapulae and posterior clinoid processes. Areas of different density may be seen and transverse bands or striations near the ends of long bones are common. These are seen particularly in the phalanges, metacarpals, metatarsals, fibulae and tibiae. In these same bones and in the ribs are sometimes seen more

or less clearly defined, rounded, or oval opaque islands or spots. There have also been noted especially in the calcaneum, small clear areas where the bone is invisible, appearing as holes in the skeleton. Old fractures may be seen and the cartilages appear more calcified than normal.

As has been stated, nearly all cases of this disease are discovered accidentally when roentgen-ray pictures are made of some bone. In early life most of them are diagnosed as rickets and so treated. Syphilis is often suspected and many are given antisyphilitic treatment in spite of a negative Wassermann. In older patients the condition is generally discovered on account of fractures from slight trauma. The striking opacity of the skeleton showing the structureless, silhouette-like shadow is characteristic.

Congenital osteosclerosis can be rapidly fatal, and it is probable that many cases die in utero and others shortly after birth. In those that survive, the condition becomes chronic and it sometimes seems to become arrested. The outcome depends largely upon the development of secondary manifestations such as anemia and hydrocephalus. The fractures finally heal, hydrocephalus causes its usual symptoms, and optic atrophy leads to blindness. A leukemic picture seems to give a bad prognosis.

There is no cure. Careful oral hygiene should be carried out since necrosis of the jaw has terminated many cases. Calcium phosphorus, cod liver oil, irradiated ergosterol or any other substance that promotes the growth of bone should be avoided. Iron may help the anemia. Persons with the condition should not bear children.

CASE REPORT

W. S. K., male, three and one-half years old, came in because of blindness, enlargement of the head and inability to walk.

History. Father living and well, 26 years of age. Mother living and well, about the same age. She had one ovary, a Fallopian tube and the appendix removed after being married about five months. While she was pregnant with this child and during a later pregnancy she had a great deal of trouble with her teeth—all the fillings came out. She had a Cesarean operation when the patient was two and one-half years old. The baby thus delivered was said to be normal in appearance but died about four hours after delivery from atelectasis. There is no history of any known relatives having a condition similar to that of the patient. The father's blood Wassermann was negative and the mother's was reported to have been 2 plus at one time. The mother had a great deal of nausea and vomiting preceding the birth of the patient and almost miscarried several times. She was given some kind of intravenous medication for this. The mother thought the child was born about two weeks prematurely. There was a prolonged, dry labor but no instruments were used. The baby was blue and difficult to revive. Weight, 8½ pounds. A moderate degree of icterus developed and lasted for a few days. Breast-feeding was carried out for five months but the infant did poorly until weaned. Cod liver oil and orange juice were begun at three months. At this time the spleen was known to be enlarged. At six months it was noticed that the eyesight was poor and that the eyes rolled more or less constantly. At five months the two lower central incisors came through and soon afterwards the two upper central incisors. No other teeth have erupted but the gums have become swollen several times and were once lanced by a physician. At six or seven months

the child could sit upright and soon learned to scoot along on the floor. He has never walked except when supported or with the aid of braces. He began to talk at an early age and has been very alert mentally, with an unusually good memory and a good vocabulary. A prolonged attack of whooping cough occurred at two years. At two and one-half years he was quite ill with a high fever for about two weeks and was said to have "congested lungs" and an "abscessed spleen." He had a course of ultra-violet ray treatments at about five months with some roentgen-ray exposures over the spleen and some intramuscular antisyphilitic treatments afterwards. Another course of ultra-violet ray treatments was given at 18 months. Cod liver oil and viosterol have been used persistently. The appetite has been generally good and he has had a satisfactory variety of food. He has always slept fairly well except when the intracranial pressure seemed increased. There has been good control of the bladder. The patient has usually shown a feeling of well being and a cheerful disposition.

Examination Weight, 28.5 pounds. The head appeared large and the fontanelles were closed, but there appeared to be some separation of the sutures. The bosses were very prominent. There was no vision except for the ability to distinguish light from dark. The pupils reacted fairly well to light. The skin and mucous membranes were very pale. There was a marked condition of genu valgum with a great deal of curving of the tibiae. The spleen was enormously enlarged and very hard. The liver was enlarged to a lesser extent. The abdomen was large and of irregular contour due to the large spleen and liver. There were only four teeth (two upper and two lower incisors). The general musculature was very flabby. Both optic nerves showed almost complete atrophy. No disturbance of the general nerve reflexes was noted.

Laboratory Blood Hemoglobin 60 per cent. Total erythrocytes 2,620,000. Total leukocytes 14,000. Neutrophils 38 per cent, lymphocytes 60 per cent, eosinophiles 1 per cent, basophiles 1 per cent. Anisocytosis, poikilocytosis and polychromatophilia were noted. Wassermann and Kline tests were negative. Blood calcium 14.4 mg, phosphates 5.4 mg. Spinal fluid withdrawn under greatly increased pressure, cell count 2, Wassermann and Kline tests negative, colloidal gold curve 2100000000. The urine was negative except for a very low specific gravity. Roentgen-ray showed marked density of bones all over the body, an increased thickness of the cortex with little or no medullary space—typical of marble bone.

Course The patient lived about 15 months after the first examination. His condition changed little. During part of this time he had purpuric spots over his body and there was some difficulty with bleeding from the gums. Death was due to an accidental fall with possible intracranial hemorrhage. No autopsy was permitted.

COMMENT

This case presented most of the characteristics which are typical of the disease. Symptoms showed up sufficiently early to make it seem possible that the condition was present at birth. The difficulty of diagnosis is well illustrated. He was seen early by competent physicians and was treated for rickets and syphilis. We accidentally diagnosed the case by having a roentgen-ray picture made while looking for some other condition. It is not at all improbable that the later baby, that was delivered by Caesarian section and that lived only a few hours, had the same condition. The patient got along quite well considering the fact that there was almost no bone marrow space visible in the pictures and that there was consequently a marked anemia. One must conclude that the great enlargement of the liver



FIG 1

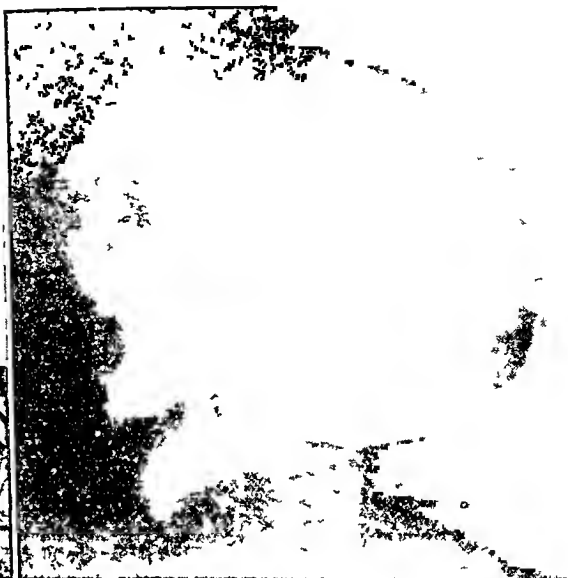


FIG 2

FIG 1 Patient 4 years of age, showing characteristic features, large head, eyes widely separated, sunken nose with broad tip. Markings show moderately enlarged liver and enormously enlarged spleen. Marked genu valgum.

FIG 2 Roentgen-ray of skull. Brings out the marked density of the bones.



FIG 3



FIG 4

FIG 3 Roentgen-ray of spine showing marked density.

FIG 4 Roentgen-ray of pelvis, femora, one tibia and fibula showing the structureless opacity of these bones and the localized thickenings over lower ends of femora.

and spleen must to some extent be due to the resumption by these organs of their hematopoietic functions, in order to compensate for the loss of bone marrow

SUMMARY

Congenital osteosclerosis or marble is a rare condition but probably occurs more frequently than is generally believed. The cases that are correctly diagnosed are usually discovered more or less accidentally while looking for other conditions. In early life most of them are treated at some time or other for rickets and syphilis. The diagnosis is easily made by taking x-ray pictures of the bones. There is no satisfactory treatment, but the condition sometimes seems to become arrested. The outcome depends largely upon such secondary symptoms as anemia and hydrocephalus. A case report is presented.

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CATHARSIS IN ACUTE UPPER RESPIRATORY INFECTIONS ¹

By FRED N. MILLER, M D , *Eugene, Oregon*

SINCE the various factors involved in the etiology of the common cold and of grippal infections are at best imperfectly understood, it is not surprising that the therapeutic management of acute upper respiratory disorders has not been satisfactorily established. Present treatment is largely a melange of traditional procedures which are varied from time to time usually only in minor details. The evaluation of any therapeutic procedure or agent in the treatment of these infections is especially difficult for two reasons. In the first place there is a considerable variation in the manifestations of respiratory infections not only from season to season but from month to month. Anyone who has a considerable practice with this type of affection soon is impressed with the fact that the virulence measured either by the extent of the prostration or the number of complications varies tremendously in any community sometimes in one or two weeks. A second difficulty in the proper evaluation of a therapeutic remedy or procedure in the upper-respiratory infections is due to the fact that such infections as a rule run a relatively short course and tend to clear up spontaneously. Nevertheless because of the great prevalence of these infections and the resultant morbidity and economic loss, and because of the complications and sequelae which are so frequently serious, it is important to analyze in as critical a manner as possible the management of these infections.

One of the most common practices of physicians, in the past at least, has been to administer a cathartic either at the onset of a cold or soon thereafter. The importance of "keeping the bowels open" is practically always stressed in the advice given to the laymen and is not infrequently advocated in textbooks of medicine and in current medical literature. Because of the frequency with which a cathartic is prescribed or administered for a cold, and because of the importance of a proper evaluation of the treatment of acute upper respiratory infections, it seemed desirable to attempt to get some evidence as to the value of catharsis in these conditions.

Infirmary or bed patients were chosen because of the possibility for control. Previous experience with ambulatory university students had demonstrated the practical difficulty of having them return for observation or the even greater difficulty of assuring their following directions. Infirmary patients are under strict control and it was therefore considered that the alternate case method might satisfactorily be applied to these patients.

Cases were chosen in which the nose, throat, trachea and upper bronchi were affected and in whom there was no demonstrable complication nor any gastrointestinal disturbance and a relatively few cases were chosen each

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From the Student Health Service, University of Oregon

year since 1927, to allow for seasonal variation in virulence. Cases chosen for this study were put on "routine upper respiratory orders" and the Infirmary nurses were instructed to have all such cases fill out the following questionnaire

QUESTIONNAIRE FOR STUDENTS WITH COLDS

Please fill out questionnaire carefully. Colds in the head and chest are very common among students and we are anxious to study the results of our treatment carefully so that we can treat these conditions in the best possible way

- 1 How many days have you had a cold or been sick?
- 2 Do you feel sick all over?
- 3 Does your head ache?
- 4 Are you tired or all worn out?
- 5 Did your bowels move today? Yesterday?
- 6 Have your bowels been moving as well as usual during the past week?
- 7 Have you taken a cathartic in the last three or four days?
- 8 Do you usually take a cathartic for severe colds? If so, are you strongly of the opinion that it helps you?

Roughly one-third of the cases had already taken a cathartic before presenting themselves to a doctor at the Health Service. The alternate cases of those who had not previously taken a cathartic were then given one ounce of magnesium sulphate (a few students refused and a few others were missed by the nurses). Other treatment was largely symptomatic—salicylates for malaise, ephedrine for the nose, Dobell's gargle, steam inhalations and codeine for cough were commonly employed but always without any knowledge on the part of the prescribing physician as to whether or not the patient had received a cathartic. At the end of the experimental period (1927 to 1934) the cases were divided into three groups and the results are tabulated in table 1

TABLE I

| | No | Average Max Temp | Average Hosp Days |
|--|----|---------------------|----------------------|
| Students who had taken a cathartic previous to admission | 88 | 100.17 | 4.12 |
| Students who were given 1 oz. of magnesium sulphate | 70 | 100.12 | 4.36 |
| Students who were given no cathartic | 99 | 100.05 | 4.12 |

It is felt that both the maximum temperature and the number of hospital days are at least fairly objective criteria and therefore are proper measures of the effect of catharsis since catharsis was produced in 69 of the 70 (98.5 per cent) given magnesium sulphate.

It is interesting to note that 102 (40 per cent) of the 257 state they usually take a cathartic for a severe cold but only 84 are strongly of the opinion that a cathartic really helps them. It is possible that the percentage of the general population that takes a cathartic for a severe cold is even greater than the 40 per cent found in this group.

CONCLUSION

Catharsis taken early or at the time of admission to a university Health Service Infirmary had no effect in acute upper respiratory infections as measured by the maximum temperature or the hospitalization time.

EDITORIAL

*HOW SEX AFFECTS THE INCIDENCE OF DISEASE AND MORTALITY**

ALMOST everyone who reports any considerable number of cases representative of a certain disease mentions the incidence by sex. When significant differences exist, and when an explanation is attempted, it is almost invariably based on extraneous or environmental factors. Following this general plan pregnancy and obesity are said to cause the greater incidence of diseases of the gall-bladder among females, and alcoholism explains the predominance of males among those who have hepatic cirrhosis, the ratio of males to females in these two conditions, however, is about the same whether one is considering children or adults. It is apparent, therefore, that obesity, pregnancy, and alcoholism are not the factors responsible for the interesting incidence of these diseases by sex.

A study has been made of the incidence by sex in approximately 300,000 cases of disease affecting structures which have tissues and functions common to both sexes¹. All of the diseases of the digestive tract that were studied affected males predominantly, except cholelithiasis, cancer of the gall-bladder, carcinoid tumor of the appendix, and gastric ulcer. Of the diseases of the respiratory tract and upper part of the digestive tract, only pulmonary tuberculosis of children affects females more frequently than males. Cancer of the lip, larynx, tongue, tonsils, bronchi, and pharynx, and pneumonia, actinomycosis, asthma, and bronchiectasis are predominantly diseases of males. Degenerative and inflammatory diseases of the arteries, and blood dyscrasias such as leukemia, pernicious and splenic anemia, and polycythemia affect males more often than females. Syphilis of the heart, meninges, skin and mucous membranes, and of the central nervous system much more frequently follows primary infection of males than of females. Of diseases of the bones, joints, and urinary tract, only chronic infectious arthritis affects females more commonly than males, whereas gout, malignancy of the bladder, kidney, and bones, osteomyelitis, renal tuberculosis, glomerular nephritis, renal stone, and tuberculous arthritis affect males predominantly.

A reversal of the incidence of diseases by sex is noted in functional disturbances such as Raynaud's disease, migraine, hysteria, chronic nervous exhaustion and biologic inferiority, by which conditions females are more commonly affected than males. Data show that four men commit suicide to each woman, although women make more suicidal "attempts" than men.

These studies in morbidity indicate that males are less favorably situated as far as serious organic disease is concerned. This fact should influence comparative expectancies of life and the percentage distribution of males and females in the entire population. Figures for 1927 reveal that, at the age

* Submitted for publication January 3, 1935

¹ ALLEN, E. V. The relationship of sex to disease, *ANN. INT. MED.*, 1934, **11**, 1000-1012

of 10 years, girls could expect 55.32 years of life and boys only 51.88 years. The 1920 census figures for the registration area of the United States show that, after the age of 55 years, there is a gradually diminishing predominance of males in the population until, at the age of 75 years, the women outnumber the men and continue to do so in the more advanced ages. Of the centenarians in the United States in 1920, almost twice as many were women as men.

The factors which are usually set down in explanation of the greater incidence of organic disease and mortality among males are overwork, alcoholism, venery, tobaccoism, exposure to the elements, industrial hazards, and irregular habits of eating and drinking. The validity of these banal theories may be tested in two series of observations regarding the influence of sex on mortality, in both of which extraneous factors are entirely common to both sexes and, therefore, negligible.

In the registration area of the United States in 1920, 8,500 males and 6,700 females died for each 100,000 males and for each 100,000 females, respectively, of that part of the total population which was less than one year of age. Similar predominant mortality existed for males of all ages less than 20 years. This condition was likewise true in the census years 1900, 1910, and 1930. It would be difficult logically to attribute the greater susceptibility of infant and adolescent males to fatal disease to extraneous factors, as they appear to be exposed to about the same environment as females of similar age. An even better control is the intra-uterine period of life. The mortality rates for males during intra-uterine life is consistently higher, varying with the different months after conception from 375 to 118 males for each 100 females.

Further inquiry into the effect of habits and environment on differential sex mortality is aided by observations relative to animals.² Studies of fish reveal that, as a result of the greater incidence of death among males, there is an increase in the ratio of the number of females to the number of the males as the age of the fish increases. If both sexes of swordtail minnows of equal age are subjected to deleterious solutions, such as potassium cyanide and alcohol, the males invariably succumb first. Conclusions of a similar nature apply to meal-worm beetles, fruit flies, decapods, schizopods, amphipods, spiders, insects and copepods. The observations regarding the last mentioned are amusing. The males are dwarfs which attach themselves to females of their own age and litter and cling to them all their lives. Even this parasitic existence does not protect the male from death at a comparative youthful age.

Two conclusions from such data are inevitable: *the male of both animals and humans is inferior in constitutional vigor and vitality, and this inferiority is internal and constitutional and not external or adventitious.*

² - ALLEN, E. V. The difference in mortality of animals by sexes, Proc. Staff Meet. Mayo Clinic, 1933, VIII, 755-757.

The cause of the inferiority of the male is far from apparent. The theory that the usual unmatched chromosome of males is etiologic is refuted by evidence that certain species of females with an unmatched chromosome are superior to males.

The apparent higher metabolism of males, as exemplified by the sperm which is small, active, and energy-expending in contrast to the ovum which is large, quiescent, and energy-storing, is a far from satisfactory explanation. Inscrutability relative to cause exists now, and we suspect, will continue to exist. This state need not detract from the fact that sex-linked inferiority of the male is incontrovertible. *There seems no doubt that, speaking comparatively, the price of maleness is weakness.*

E V A

REVIEWS

Atlas Fundus Oculi By WILLIAM HOLLAND WILMER, M D, LL D, Sc D, Professor of Ophthalmology of Johns Hopkins University and Director of the Wilmer Institute, with an introduction by Warfield T Longcope, M D 225 X 285 cm The Macmillan Company, New York 1934 Price, \$35 00

This volume includes 100 colored plates of normal variations and pathological conditions of the fundus oculi as seen by the author in his extensive and varied experience

In the introduction Dr Longcope points out the value of the ophthalmoscope to the internist in that the finer vessels can be studied which is a great aid in the differential diagnosis of various vascular diseases as well as a help in diagnosing blood and kidney conditions suppurative processes, etc

The author describes in detail the method of using the ophthalmoscope and the various points to be studied He points out the normal variations that may be found in the color of the fundi of different races also the variations in the color of the nerve head with its physiological cup

The main portion of the work consists of the 100 colored plates which are accurately reproduced in color from original colored drawings made of the patient by the staff artist of the Wilmer Institute, Mrs Annette Burgess Opposite each plate is a brief description of the case giving the history with both laboratory and ophthalmological findings and its diagnosis In several instances a plate is shown of a case at the inception of the condition and another plate of the same case after treatment had been inaugurated

While other excellent atlases of the fundi oculi have been published, especially that of Frost, none have attained the perfection in reproduction or shown the great variety of lesions that the present atlas presents

The author, the artist, the engravers and the publishers should all be congratulated upon this superb work which undoubtedly will remain as a standard for many years Every oculist and every internist who is constantly making differential diagnoses should have this volume for reference when studying the fundus oculi

C A C

Cataract Its Etiology and Treatment By C A CLAPP, M D, F A C S, Professor of Ophthalmology University of Maryland, Associate Professor of Ophthalmology Johns Hopkins University, Foreword by Dr William H Wilmer 254 pages Lea and Febiger, Philadelphia 1934 Price, \$4 00

Since cataract is one of the most frequent causes of poor vision in the old and not infrequently in the younger patient, its etiology, prevention, and treatment are of vital interest to every ophthalmologist and internist This volume, "Cataract, Etiology and Treatment" is, it would seem, the rare combination of a wealth of facts in comprehensive form, collected into the smallest space feasible It contains in addition to what the title implies, chapters on the development, comparative anatomy, anatomy, nourishment and growth, physiology and chemistry of the normal lens, and congenital anomalies of the lens other than cataract The chapters on the development of the lens and the comparative anatomy of the lens were written by Ida Mann of London

Some of the more practically inclined may criticize certain portions chiefly the chapter on the chemistry of the lens, and portions of the chapter on etiology, as being too scientific for a volume of this nature, but the patience of these will be amply rewarded by the very practical and thorough discussion of treatment

As seen from the size of the bibliography, a vast amount of literature has been covered in the preparation of this monograph. The ideas and theories of various workers, often conflicting are clearly presented, and these should serve as a stimulus to further research. Those students particularly interested in the chemistry and physiology of the lens will find facts of interest to them.

The volume should appeal to the investigator, the practitioner of ophthalmology and the internist who wish a compact work on the crystalline lens.

H F G

Periodic Fertility and Sterility in Woman—A Natural Method of Birth Control By Professor HERMANN KNAUS, Head of the Clinic for Gynecology and Obstetrics of the German University of Prague, Foreword by Professor F H A MARSHALL, F R S, Cambridge, England. Authorized English Translation by D H KITCHIN and KATHLEEN KITCHIN, M Sc, M B, B S, London. 162 pages, 17.5 × 24.5 cm, 64 illustrations and 12 tables. Wilhelm Maudrich, Vienna (book obtainable in U S A and Canada through the Concup Company, Hobart, Indiana). 1934. Price, \$6.00.

Both physicians and laymen are now giving much thought to the so-called "safe period," and the subject is being so universally discussed that this translation of Professor Knaus' comprehensive book on "Periodic Fertility and Sterility in Woman" should be read with interest by great numbers of English-speaking people.

Dr Knaus started his study of the physiology and pharmacology of the uterine muscle in 1924, and in 1927 he discovered a reaction of the uterine musculature by means of which the exact day of ovulation can be determined. Through this investigation and through studies on the viability of the human ovum and spermatazoa, Dr Knaus concludes that in women with regularly recurring menstrual periods conception can occur during only five days of a menstrual cycle. However, in order properly to determine the days on which conception can occur it is necessary for a woman to keep a very exact record of the days of onset of several successive menstrual periods. The author emphasizes that those women who do not menstruate at regular intervals must be considered to be fertile for more than five days of the cycle. Nevertheless, he feels that it is possible to determine the period of fertility and sterility in practically all women.

Some gynecologists do not believe that this method of birth control is as infallible as it is stated to be in this book, but it must be remembered by all critics that no other method is absolutely certain. Dr Knaus claims that the few reported failures that have followed the use of this method of birth control have all been due to women not keeping exact records of their menstrual cycles.

This book has been interestingly written and well translated into English. The author makes of his subject an almost continuous story which holds the reader's interest throughout the entire 148 pages of text. At the back of the book are 14 pages of bibliography which include practically all the important articles which have been written on this subject. Not only the gynecologists and the physiologists should become fairly familiar with Dr Knaus' work but also the general practitioner, for it is to the latter that women usually go to make inquiries about the safe period.

L B

Conception Period of Women By KUSAKU OGINO, M D, Head of the Gynecological Section of Takeyama Hospital, Niigata, Japan. 94 pages, 12.5 × 19 cm. Medical Arts Publishing Co., Harrisburg, Pennsylvania. 1934. Price, \$1.00.

This booklet, written by a Japanese gynecologist, has received considerable publicity throughout the United States. The last 10 pages are a reprint of an article

by three American physicians, A G Miller, C H Schultz and D W Anderson, which appeared in the June 1933 issue of *Surgery, Gynecology and Obstetrics*. This article essentially covers all the points presented by Dr Ogino.

It is obvious that Ogino has formed his conclusions from a very small number of cases, and that although his arguments are very logical he has not ruled out entirely the possibilities of error. Nevertheless, his conclusions are interesting and his diagrams are well got up.

He states that "the period of ovulation is from the twelfth to the sixteenth day before the subsequent menstruation, having no connection with the length of menses. The human conception period is in the eight days from the twelfth to the nineteenth day before the subsequent menstruation." He gives as the formula for calculating the conception period

The first day of the conception period = 10 plus the number of days of the minimal cycle — 28

The last day of the conception period = 17 plus the number of days of the maximal cycle — 28"

The final conclusion, therefore, is that if coitus is indulged in outside of the conception time there is no danger of pregnancy.

J L McC

The Heart Visible By J POLEVSKI, M D, Attending Physician and Cardiologist, Newark Beth Israel Hospital. 207 pages, 16 × 23.5 cm. F A Davis Co, Philadelphia. 1934. Price, \$5.00.

This volume deals with the roentgenologic study of the heart. It is divided into six parts: General Considerations, Methods of Roentgenologic Study, The Normal Heart, The Abnormal Heart, The Pericardium, The Great Vessels. It contains 122 diagrams and reproductions of films. These are, on the whole, excellent. The author points out the futility of depending upon a single antero-posterior view of the heart for the purpose of roentgenologic study and diagnosis, and of depending upon simple transverse measurements of the heart in arriving at a decision as to the normality of the heart. Complete fluoroscopic examination is stressed. Some information in regard to the history of the patient and the ability to use a stethoscope is advocated for the roentgenologist in order for him to be of the greatest possible help in arriving at a diagnosis. This volume is recommended to cardiologists and roentgenologists and all others interested in the subject.

W S L, JR

Body Mechanics in the Study and Treatment of Disease By JOEL E GOLDTHWAIT, M D, LL D. 281 pages, 14 × 20.5 cm. J B Lippincott Co, Philadelphia. 1934. Price, \$5.00.

In the preface the author offers a just criticism of the whole medical profession, to wit, that the profession does not give the chronic patient a fair "break", so much attention is paid to the causes, diagnosis, and treatment of the acutely ill patient that the one who does not respond promptly is slowly pushed aside and preferably forgotten. Poor bodily mechanics will certainly play a far greater role in the chronic patient than in the acute one, and this factor is quite apparent to those of us who treat chronically ill people. In general also it is a well known fact that improved posture and bodily tone make for better health.

In Chapters 5 to 9 inclusive the author has shown how poor bodily mechanics to a large degree may cause most of the chronic ailments of the individual, even those

which have ordinarily been considered of infectious type. The author's long experience with postural conditions lends weight to his statements on this subject.

The chapters on treatment reveal nothing particularly new to those who have been following the developments in physical therapy, but they do outline a series of exercises, etc., which will certainly improve a patient's general physiological activities and in so doing react favorably on many pathological conditions.

The cases reviewed in the last two chapters lend strength to the theory and proof to the statements made in the earlier chapters. The results obtained are very striking.

The presentation of the subject loses some of its force because of a certain vagueness in the author's phraseology. The book as a whole, however, will convince most physicians that in the treatment of the chronic patient a sane and intelligent application of the methods of physical therapy is a very valuable adjunct to other forms of treatment.

A F V

COLLEGE NEWS NOTES

NEW LIFE MEMBERS OF THE COLLEGE

The College is gratified to announce that the following Fellows have become Life Members by contributing the specified fees for their respective ages to the Endowment Fund

| | |
|---------------------------------------|-----------------|
| Dr Ralph O Clock, New York, N Y | January 1, 1935 |
| Dr Charles F Morsman, Hot Springs S D | " 1, 1935 |
| Dr Lawrason Brown Saranac Lake, N Y | " 11, 1935 |
| Dr Grant O Favorite, Philadelphia Pa | " 11, 1935 |
| Dr James Alex Miller, New York, N Y | " 12, 1935 |
| Dr Edward C Klein, Jr, Newark, N J | " 14, 1935 |

Some years ago the Board of Regents, believing a sound financial foundation to be one of the best guarantees of insuring the stability and perpetuity of the American College of Physicians, provided for the building up of an Endowment Fund, "the principal of which shall be held intact and invested in securities approved by the Board of Regents, while the income shall be available for carrying out the purposes of the organization"

The Endowment Fund had reached a total of \$55,640 00 on December 31, 1934, income from which has materially helped in carrying on the work of the College during the recent years Especially has the income contributed toward special activities of the College, such as the stimulation of research through the awards of the Phillips Memorial Prize and the Research Fellowship of the College, established during the past year

Until 1933, the Life Membership fee amounted to \$500 00 A careful study, from an actuarial standpoint, led the Board of Regents to adopt a new plan during the early part of 1933 by which a Fellow or Master may be accorded Life Membership up to 45 years of age by the payment of \$300 00 in addition to the Initiation Fee paid at the time of election From 45 years of age to 58 years of age, a Fellow or Master shall pay an amount equivalent to the total amount of dues he would ordinarily pay from his present age to the age of 65 years From the age of 58 forward, the minimum Life Membership fee is \$100 00, in addition to the original initiation fee

The Life Membership Fee entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Clinical Sessions, and to the official publications of the College, including the Directory and the ANNALS OF INTERNAL MEDICINE An official Life Membership Certificate is issued to each new Life Member, and his name is engrossed on the permanent scroll of Contributors to the College Endowment Fund

Quite aside from any personal advantages which Life Membership confers, members who can afford to do so should subscribe for the express purpose of putting the College in position, financially, to broaden its activities along lines which are clearly suggested at this time, when there is so much conflict of thought and opinion on the subjects of medical practice, medical fees, medical education, and other topics which are of primary interest to internists

The plan is sound financially, both from the standpoint of the College and of the member It affords the member an opportunity of paying his full dues during his productive years and while his income is largest, thus avoiding the burden of dues later in life The plan provides a means for underwriting dues years in advance, but of receiving the premium of active membership throughout one's entire life A member pays no more for Life Membership than he would pay for ordinary active membership to 65 years of age, without active membership thereafter (ordinary

members, upon reaching the age of 65, are entitled to the waiver of their dues for the balance of their lives, but, in effect, they become inactive members, because they do not receive the Journal, the Directory, or other publications, except upon direct subscription) Many members can readily afford Life Membership during their active, productive years, but, with changing conditions or ill health, find annual dues a burden in later life

Acknowledgment is made of the following gifts to the College Library of publications by members

Dr Oliver T Osborne (Fellow), New Haven, Connecticut—one book, "Mouth Infection"

Dr Arthur C Clasen (Fellow), Kansas City, Missouri—two reprints

Dr Emil F Koch (Fellow), Brooklyn, New York—one reprint

Dr Lea A Riely (Fellow), Oklahoma City, Oklahoma—four reprints

Dr Robert B Radl (Fellow), Minneapolis, Minnesota—two reprints

The 1935 Annual Clinical Congress of the American College of Surgeons will be held in San Francisco, October 28 to November 1

Dr George R Minot (Fellow), Boston, Massachusetts, addressed the Royal Society of Medicine, London, England, November 29, 1934, on "Some Aspects of Anemia," and also addressed the University of Copenhagen, Copenhagen, Denmark, December 6, 1934, on the same subject Dr Minot addressed the staff and students of Guy's Hospital, London, during the same visit, on "Pernicious Anemia and the Interpretation of Reticulocyte Responses" On December 12, at the Caroline Institute, Stockholm, Sweden, Dr Minot delivered a Nobel Lecture on "The Development of Liver Therapy in Pernicious Anemia"

Dr George Herrmann (Fellow), Galveston, Texas, is Chairman of the Section on Medicine of the Southern Medical Association for the year 1934 to 1935, ending with the meeting of that society in St Louis, Missouri, during November of this year

Dr James Murray Washburn (Fellow), Chicago, retired during the past summer from active practice Dr Washburn has founded at Lake Lure N C, not far from Asheville, an institution called "The Chalet," which will care for a limited number of men patients who are in need of rest and recuperation

Dr J L McCartney (Fellow), who has entered the private practice of psychiatry in Portland, has taken charge of a new psychiatric institution in that city known as "The Northwest Retreat" the purpose of which is to care for neurotic individuals who are in need of intensive psychotherapy

Dr Leila E Andrews (Fellow), Oklahoma City, Okla, addressed the Tulsa County Medical Society at Tulsa Okla, on November 12, 1934 Her subject was "Calcium Deficiency"

ABRIDGED MINUTES OF THE BOARD OF REGENTS, PHILADELPHIA, PA.,
 DECEMBER 16, 1934

The Board of Regents of the American College of Physicians met and was called to order at the College Headquarters, Philadelphia, Pa., at 10 00 am December 16, 1934, by the President Dr Jonathan C Meakins

Those present were Dr Jonathan C Meakins Dr James Alex Miller Dr James H Means, Dr William D Stroud, Dr Randolph Lyons, Dr William Gerry Morgan, Dr David P Barr Dr James B Herrick, Dr Clement R Jones, Dr S Marx White, Dr Walter L Bierring, Dr John H Musser, Dr O H Perry Pepper, Dr Luther F Warren Dr Roger I Lee, Dr Sydney R Miller, Dr George Morris Piersol, Dr Maurice C Pincoffs, Dr Ernest B Bradley In addition, there were present Dr Charles F Martin, Chairman of the Finance Committee, Dr Charles G Jennings, member of the Committee on Public Relations, Dr Charles H Cocke, member of the Committee on Credentials, Dr Alfred Stengel, General Chairman of the forthcoming Philadelphia Clinical Session, and Mr E R Loveland, Executive Secretary

The Executive Secretary acted as Secretary of the meeting

An abstract of the Minutes of the meetings of the Board of Regents held during the Chicago Clinical Session was read and approved

After brief comments by President Meakins, Secretary-General Morgan presented the following communications

(1) A set of resolutions from the Chicago Roentgen Society dealing with a matter of bringing from foreign countries physicians in different specialties who were said to be displacing competent American physicians in hospital appointments

On motion by Dr Bierring, seconded by Dr Jones, and regularly carried, it was *Resolved*, that the communication from the Chicago Roentgen Society be received and filed

(2) A letter and set of resolutions from the Committee on Health and Public Instruction of the St Louis Medical Society dealing with the discontinuance of the Reserve Officers' Training Corps Units in medical schools, and petitioning the re-establishment of the Corps as soon as possible

On motion, seconded and regularly carried, it was

Resolved, that the communication be received and filed

(3) A letter from Dr W A Stauffer, of Elkhart, Ind., offering to present to the College certain medical books

Upon motion, seconded and regularly carried, it was

Resolved to thank Dr Stauffer for his offer to present the books to the American College of Physicians, but to suggest that the books be donated to some other regular medical library, inasmuch as the books in the Library of the American College of Physicians are those of which our own members are the authors

On individual motions the following resignations were accepted

Associates

Thomas J Burrage, Portland, Maine

J C Burkle, La Fayette, Ind

J Alexander Clarke, Jr., Philadelphia, Pa

H H Heuston, Boulder, Colo

Fellows

Bartgis McGlone, Philadelphia, Pa

Giuseppe Vercellini, Los Angeles, Calif

The Executive Secretary then presented certain communications concerning special cases affecting fees and dues, the cases being acted upon individually by the Board of Regents

President Meakins announced the names of ten Associates who had been dropped from the roster of the College because their Associateship period of five years had expired without their qualifying for Fellowship

He announced further the names of ten Fellows and two Associates whose names had been returned to the roster of the College because they had paid up their delinquent dues of two years' standing

The Executive Secretary reported the receipt of letters of regret at inability to attend this meeting from Drs Crispin, Churchill, Elliott, Kerr, Pottenger and Richards. He further read a communication from Dr Dwight O'Hara, of Boston, and from Dr Frank R Starkey, of Philadelphia, which required no action

President Meakins reported the following deaths among Associates and Fellows of the College since the last meeting of the Board of Regents

Associates

| | |
|-------------------------------------|--------------------|
| George M Gilchrist, Groton, N Y | August 25, 1934 |
| James L Junk, Connellsville, Pa | May 20, 1934 |
| True E Makepeace, Farmington, Maine | November 6, 1934 |
| Curran Pope, Louisville, Ky | September 21, 1934 |

Fellows

| | |
|---------------------------------------|--------------------|
| Bailey K Ashford, San Juan, P R | November 1, 1934 |
| Isidor David Bronfin, Denver, Colo | July 31, 1934 |
| Claude E Case, Clifton Springs, N Y | January 27, 1934 |
| Merchant William Colgin, Waco, Tex | July 15, 1934 |
| Addison E Elliott, San Diego, Calif | April 9, 1934 |
| Benjamin Gutmann, New Brunswick, N J | August 7, 1934 |
| G Walter Holden, Denver, Colo | July 12, 1934 |
| James Edwin Houghton, Washington, D C | May 3, 1934 |
| Morris H Kahn, New York, N Y | July 13, 1934 |
| Hugh Mackay, Winnipeg, Man, Can | October 12, 1934 |
| Thomas E Satterthwaite, New York, N Y | September 19, 1934 |
| Paul Galpin Shipley, Baltimore, Md | September 12, 1934 |
| John Peter Zohlen, Sheboygan, Wis | June 2, 1934 |

The Executive Secretary then presented the following resignations, which were acted upon as indicated

Associates

Thomas J Burrage, Portland, Maine

Upon motion by Dr Bierring, seconded by Dr White, and regularly adopted, it was

Resolved, that the resignation of Dr Thomas J Burrage be accepted

J C Burkle, La Fayette, Ind

Upon motion by Dr Pepper, seconded by Dr James Alex Miller, and regularly adopted, it was

Resolved, that the resignation of Dr J C Burkle be accepted

J Alexander Clarke, Jr, Philadelphia, Pa

Upon motion by Dr White, seconded by Dr James Alex Miller, and regularly adopted, it was

Resolved, that the resignation of Dr J Alexander Clarke, Jr be accepted

H H Heuston, Boulder, Colo

Upon motion, seconded and regularly adopted, it was

Resolved, that the resignation of Dr H H Heuston be accepted

Fellows

Bartgis McGlone, Philadelphia, Pa

Upon motion by Dr White, seconded by Dr James Alex Miller, and regularly carried, it was

Resolved, that the resignation of Dr Bartgis McGlone be accepted

Dr George Morris Piersol, Chairman of the Committee on Credentials, reported that his Committee had met on December 15 and had examined the credentials of the candidates for Associateship and Fellowship. Of 73 candidates for Fellowship, the Committee presented to the Board of Regents the names of 58 recommended for election to Fellowship and seven for election to Associateship, instead of Fellowship. Of 109 candidates for Associateship, the Committee presented to the Board of Regents the names of 86 recommended for election to Associateship. (Editor's note: The list of physicians elected to Fellowship and Associateship was published in the January 1935, issue of this journal.)

Chairman Piersol then presented the case of Dr Paul John Hanzlik, of San Francisco, Calif., who is a full-time teacher. He was elected a year ago subject to the customary reduction in fees and dues, but Dr Hanzlik had written a letter stating that for financial reasons he could not avail himself of the election if he had to pay an initiation fee, contending that like Dr Addis he should be granted a waiver of such fee.

Upon motion by Dr Warren, seconded by Dr Bierring, and regularly carried, it was

Resolved, that the initiation fee of Dr Paul John Hanzlik be waived for financial reasons and his dues be reduced to \$10.00 per annum.

Chairman Piersol then presented the case of Dr Neuton S. Stern, of Memphis, Tenn., who was elected a Fellow of the College in 1926, but who had been unable to pay the initiation fee and take up his Fellowship for financial reasons. Dr Stern had sent his check for \$100.00, along with an application.

Upon motion by Dr Piersol, seconded by Dr James Alex Miller, it was

Resolved, that Dr Neuton S. Stern's application for the reinstatement of his name on the Fellowship Roster be approved as of the present date, and that his initiation fee be accepted.

Chairman Piersol then read a communication from the Executive Secretary concerning the number of candidates that are elected, both to Fellowship and Associateship, but who are slow to take up their election by the payment of the required fees. After general discussion by members of the Board, it was the consensus of opinion that the Executive Secretary should work out a plan with the proposer, possibly by having a statement added to the application form, or enclosed in the letter of acknowledgment of the receipt of applications (under no circumstances with the candidate directly), by which it could be determined in advance that the candidate would promptly take up his election, if recommended by the Committee on Credentials.

Chairman Piersol then read a communication from the Surgeon General of the Army, Dr Robert U. Patterson, in regard to suggestions for additional or supplementary eligibility requirements for the personnel of the Medical Corps of the U. S. Army when presented for membership in the College. Dr Patterson, it was evident, was seeking a method of measuring men as the criteria for selection of candidates. After general discussion, on motion by Dr Piersol, seconded by Dr Bierring and regularly carried, it was

Resolved, that the Surgeon General of the U. S. Army be requested to get in touch with the Surgeon General of the U. S. Navy, in order to work out some scheme, mutually agreeable, for the further determination of candidates for Associateship and Fellowship from both Services.

It was suggested that this be taken up with the Surgeons General by the Committee on Credentials

Dr O H Perry Pepper, Chairman of the Committee on Examinations, reported as follows "This Committee was appointed by President Meakins following the adoption by the Board of Regents, on April 17, 1934, of a report by the Committee on Specialization, that report containing six items (see page 585, Minutes of the Board Regents) The first item stated 'in addition to the present requirements for Associateship those candidates who have been approved by the Committee on Credentials shall be required to pass a written examination in Internal Medicine' In spite of that action, your Committee on Examinations, after studying the matter and exchanging ideas by mail, have come to the conclusion that it would be impractical for this College to give an examination for admission to Associateship at this time We do think it would be feasible, perhaps, to give an examination for Fellowship, but we beg to report that the Committee believes that the following premises must be accepted (1) some improvement in the method of selection of members is desirable, (2) the College should not embark on any examination program if there is any danger of this program having to be abandoned later, either because of the difficulty of carrying it out or because of a falling off in applications, (3) any program for examination must be technically feasible, and not too discouraging to the man, and must be of dignified character, (4) the giving of examinations implies, on present figures, the examination of approximately 200 men a year, scattered throughout every State of this country and in Canada, Panama and elsewhere, (5) there is no reason to think that these examinations would not have to be given with every caution and safeguard that the National Board and College Entrance Examinations require This includes protection of papers prior to examination, proctoring during examination and proper allowance for differences of time in different geographical areas

"In view of the difficulties and dangers inherent in the giving of an examination for admission to Associateship, the Committee recommends that for the present it is inadvisable to make the attempt Every effort, however, should be made to raise the standards for admission and to improve the present machinery to that end, granting that the Board of Regents revokes its action of last spring In view of our recommendation and agreement to dispense with an examination for Associateship, the College should try to work out a scheme for examining those Associates coming up for Fellowship This would lead to our having to examine 20 per cent fewer candidates than we would deal with if the examination were for Associateship

"The Committee believes that an examination for transfer from Associateship to Fellowship is both feasible and desirable, if carried out in the following manner

- "(1) The examination to be held annually at the time and place of the annual meeting of the College
- "(2) That Associates in the third year of their membership shall be eligible to appear for examination for Fellowship if approved by the Committee on Credentials They must become Fellows within five years after election to Associateship or be dropped
- "(3) That an examination fee of \$10 00 be required for taking this examination, which fee would be deducted from the regular initiation fee in the case of successful candidates
- "(4) The examination to be the direct responsibility of a committee of five appointed by the President, the Chairman of which shall be a Regent, one member a member of the Committee on Credentials but whose other members may be selected from the membership at large It is suggested that Fellows not connected with teaching institutions be represented on this committee
- "(5) The duties of the Committee shall be the control of the examination which should be both written and practical, and the recommendation to the Regents of the successful candidates for advancement to Fellowship

- " (6) The necessary expenditures of the Examination Committee to be authorized by the Regents and included in the Annual Budget
- " (7) Examination for Fellowship shall be required of Associates elected after April 1935
- " (8) The Associates advanced to Fellowship by examination shall have the fact recorded on their Certificate in the words 'Fellowship by Examination'

"In explanation it may be added that within the five year period the Associate should attend several meetings and that the examination would therefore entail no travel or expense. By limiting the examination to advancement to Fellowship, the number of candidates will be reduced by approximately 20 per cent. By giving but one examination annually and in only one place most of the difficulties of control are avoided.

"Finally, the Committee would point out that in a few years if the examination proves efficient the College might consider the desirability of granting to those who pass this examination or perhaps a second more difficult test, some term such as licentiate, indicating their qualification as a specialist in internal medicine.

"The Committee would point out that

- " (1) The establishment of such an examination will inevitably result in limiting our future membership to those engaged in internal medicine (and pediatrics) and to the exclusion of pathologists, roentgenologists, dermatologists, many of whom are now members
- " (2) The attempt to give a practical examination may prove impractical if the number of candidates at any one examination is large
- " (3) To give a practical examination sufficiently detailed and difficult to make it worth while will entail a great deal of work and time on the part of the Committee—probably occupying their entire time during the period of the annual meeting."

Dr Pepper reported that his Committee was not unanimous in its agreement that this plan is feasible, but that the Committee has presented the plan as a program for consideration. Having the examinations at the annual meeting will avoid the necessity of giving multiple examinations. An Associate would have an opportunity of taking the examination at the third, fourth or fifth anniversary of his Associateship and that during at least one of those years the annual meeting of the College would be in fair proximity to his residence. He further commented on the fact that these examinations would probably limit future membership largely to internists and pediatricians, because he could not visualize any examination which would be appropriate for internists, pathologists, roentgenologists, etc., alike.

Dr Walter L. Bierring reported that the National Board of Medical Examiners have 50 or 60 on the Board, and that their examinations require two days and are divided into two sets. There was general discussion concerning the desirability of both a written and practical examination. President Meakins offered a brief discussion of the plan of the Royal College of Physicians. Dr James Alex. Miller discussed the possibility of substituting an oral examination in the place of a practical examination. In further discussion, Dr S. Marx White suggested the possibility of having the written examination at the annual meeting of the College and having the practical examination as a preliminary and regional matter preceding the written examination at the annual meeting.

President Meakins suggested that the examiners must be appointed by the Board of Regents and should hold office for at least five years on a rotating schedule, otherwise, there would be a variation of standards.

Dr Musser, a member of the Committee, discussed the plan at some length, pointing out his belief that the plan should be put into effect, with the exception that candidates primarily would be younger men who have set their goal to become recog-

nized internists. He advised against postponement for another year. He pointed out that we have represented in the College membership the bulwark of the outstanding internists of this country. Those who are qualified but have not sought membership probably never would under the examination plan. Dr. Musser further pointed out that the examination could be outlined with a certain proportion of grades assigned to candidates for their record of what they have done, a certain proportion for the written examination and another proportion for the oral or practical part of the examination. If the College will establish a sound foundation for certifying qualified internists, it will have far reaching effect upon the appointments to staffs in hospitals, departments of internal medicine and other institutional positions. A plan should be adopted now, in the opinion of Dr. Musser, but the initiation of the examinations may be deferred for one year.

Dr. James Alex. Miller discussed the possibility of providing means for admitting a few outstanding men without examination. It was the consensus of opinion that the Regents and Officers of the College should busy themselves in inviting any such men who are not already Fellows to associate themselves with the College during the next year, preceding the initiation of the examination, and that after the examinations are actually initiated, no exception should be made.

Dr. Piersol, on behalf of the Committee on Credentials, reiterated the fact that the present method of admission to Fellowship on case histories, autopsies, publications, etc., is not satisfactory, and that the Committee will welcome some change in the way of an adequate criterion for election to Fellowship.

Dr. Ernest B. Bradley, also a member of the Committee on Credentials, expressed some doubt as to whether members of the College can be properly chosen on written examination alone. He did not believe that a man who has been out of medical school a long time, though he may be a recognized, good internist, can pass an examination as well as a young man just recently graduated. However, there is a necessity for some new plan of admission.

Dr. James Alex. Miller suggested the value of modifying present requirements by substituting the preparation of a thesis instead of the presentation of clinical reports and autopsies.

Dr. Walter L. Bierring discussed the different Boards established, in cooperation with the American Medical Association, for the different specialties, pointing out that there will be special boards for some of the specialties affiliated with internal medicine, and that the chief concern of the American College of Physicians should be "internal medicine."

Dr. Piersol then pointed out that the American College of Physicians should be the natural certifying board to work in cooperation with the American Medical Association in the certification of internists. The College should have a definite arrangement as the certifying body for internists, and the initiation of examinations at an early date will aid us in perfecting proper machinery for this plan.

Dr. Pepper inquired of the possibility of accepting roentgenologists, for instance, as members of the College on the basis of their certification by the certifying board for roentgenologists, indicating on his Fellowship Certificate of the College the basis for his election.

Dr. David P. Barr expressed grave doubts about putting into effect the recommendations of the Committee at the present time, due to the fact that there are among our members a few who are not primarily internists, and there are among those who are recognized internists some who are not members of the College. He expressed fear that some of these recognized internists who are not already members would not be impelled to join, particularly if examinations were put into their way for qualification. He expressed some doubt also concerning the feasibility of a written examination as being adequate to determine the qualifications of a candidate. He fur-

ther pointed out his agreement with Dr Herrick that to attempt a practical examination without a large examining board would be unwise

Dr Herrick then suggested the postponement of final action on the matter until the April meeting, asking that the Committee be continued and be instructed to bring in a second report at that time He said we have made remarkable progress today in educating ourselves as to what should be done An important step of this character should not be taken by a single vote, but should be unanimous, after it has become perfectly clear what the College wants to do

Dr Pincoffs expressed the opinion that while it may not be desirable to come to a final decision at this meeting, something should be done without very much further delay It would be a mistake to have the certification of internists initiated by some other agency than the College, for that would leave the College only important from the standpoint of its annual meeting, primarily, in the minds of many men The purpose of Fellowship in the College should not simply be a certification of internists, but the establishment of a goal for which young men should work, something that will keep them studying and trying to improve and extend their qualifications

Dr S Marx White expressed agreement with Dr Pincoffs' opinions He was sympathetic with Dr Pepper concerning the need of breadth in the character of examinations He said he was inclined to view this examination as a form of "graduate examination," and the certification of Fellowship as something comparable to it The written examination should have only a small part in the determination of awarding graduate degrees Attention should be given to the character of work the candidate has done, publications should have some definite recognition If there is to be a certification of internists, that should be one of the chief functions of this College

After further discussion, it was moved by Dr Pepper, seconded by Dr White, and regularly carried, that it be

Resolved, that the Board of Regents revoke its action of April 17, 1934, concerning the initiation of examinations for Associateship

On motion by Dr White, seconded by Dr Stroud, and regularly carried, it was further

Resolved, that the report of the Committee on Examinations be accepted as one of progress, that the Committee be enlarged by the appointment of Dr George Morris Piersol, as Chairman of the Committee on Credentials, and by Dr Walter L Bierring, from the standpoint of his experience with the National Board of Medical Examiners, and that the Committee be instructed to bring back a complete report at the meeting of the Board of Regents in April

On motion by Dr Pepper, seconded and regularly carried, it was

Resolved, that the College publish in the ANNALS OF INTERNAL MEDICINE a report of progress in developing a plan for examinations to supplement the present plan of admitting members to the College, with the suggestion that the Editor prepare an editorial in the Annals expressing the consensus of opinion of the Board of Regents

Dr David P Barr, Chairman of the Committee on the John Phillips Memorial Prize, discussed the deliberations of his Committee, and presented its recommendations Inasmuch as the responsibility of the Committee had been extended to the selection of other awards than the John Phillips Prize the name of the Committee at present is inappropriate Through the Executive Secretary and Dr Pepper, a number of designs for the medal had been prepared and the Committee had decided that it would be appropriate to use the head of "Laennec," as representative of Internal Medicine, on this medal The Committee had recommended that the wording on the medal be restricted It should primarily be the award of the American College of Physicians, known as the John Phillips Memorial Award The medal should bear the Seal of the College and the name of the recipient and the year of the award should

be engraved on the outside edge of the medal. The Committee recommended a medal three inches in diameter and presented a sample for size.

Dr. Barr explained that the Committee had communicated with some 40 men, including many members of the Board of Regents, asking for suggestions concerning recipients for the award for 1935. A large number of candidates had been so obtained. The Committee had selected the recipient recommended from this group, after taking the position that it could not afford to sponsor new work which had not been completely verified, but rather that the award should be offered to a man of long standing achievement in the medical sciences, and one whose work at the present time is active and important.

The Committee also raised the question of how the Research Fellow should be selected for next year, and suggested that letters be written within one month to all the Professors of Medicine and Pediatrics in the country and to all members of the Board of Regents, asking for suggestions as to likely candidates. It had been thought last year that the machinery of the National Research Council could be used. The Committee wants to receive all these suggestions, and, if necessary, utilize the machinery of the National Research Council as well. If a candidate is proposed and is acceptable and worthy in every respect, it would not be necessary to resort to the National Research Council. If we cannot obtain a worthy candidate, the National Research Council will be very glad to present several of their candidates for our consideration. It is thought wise to use a form of application and recommendation similar to those used by the Research Council.

(To be continued)

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THE RELATION OF GASTRIC SECRETION TO HEMATOPOIESIS [†]

By THEODORE G. KLUMPP and SIMON KOLETSKY, *New Haven, Connecticut*

INTRODUCTION

IN 1833 Beaumont ¹ noted, "In febrile diathesis, or predisposition, from whatever cause—obstructed perspiration, undue excitement by stimulating liquors, overloading the stomach with food—fear, anger, or whatever depresses or disturbs the nervous system—the villous coat becomes sometimes red and dry, at other times pale and moist, and loses its smooth and healthy appearance, the secretions become vitiated, greatly diminished, or entirely suppressed, the mucous coat scarcely perceptible, the follicles flat and flaccid, with secretion insufficient to protect the vascular and nervous papillae from irritation.

When considerable, and particularly, when there are corresponding symptoms of disease, no gastric juice can be extracted, not even on the application of alimentary stimulus. Whenever this morbid condition of the stomach occurs, with the usual accompanying symptoms of disease, there is generally a corresponding appearance of the tongue."

Such changes, which usually include not only a reduction in volume of gastric juice but an absence in acidity and ferment activity, have been variably referred to as achylia gastrica, anacidity or achlorhydria. Although the literature ^{2 3 4, 5 6} records innumerable attempts to associate symptoms or disease entities such as cancer of the stomach, anemia, malnutrition, diarrhea, chronic alcoholism and cachexia with these alterations of gastric activity, nevertheless they have been found to exist in a certain percentage of otherwise normal, healthy individuals ^{7 8 9 10}. Bloomfield and Pollard ¹¹ report that 3 to 5 per cent of their clinic patients had achlorhydria and that their symptoms differed in no essential way from those of a similar series of controls with normal gastric contents. Hartfall ¹² believes that 14 per cent of the average population of all ages is achlorhydric.

Recently, however, a remarkable series of clinical observations and experiments ^{13 14, 15, 16 17 18 19} on the relationship of gastric secretion to anemia

[†] Received for publication November 16, 1934.

From the Department of Internal Medicine, Yale University, School of Medicine, New Haven.

has reopened the entire question. It is with this aspect of the problem that we are principally concerned.

ACHLORHYDRIA AND ANEMIA

Samuel Fenwick²⁰⁻²¹ in 1877 first clearly emphasized the association of atrophy of the stomach with the fatal anemia the clinical picture of which had been described by Thomas Addison²² in 1849. Other early studies recorded pathological changes,²³⁻²⁴ but Henry and Osler in 1886 were the first to describe the pathology of well documented cases.²⁵ Thereafter the association of Addisonian anemia with chronic inflammatory changes in the stomach and degeneration of the epithelial and glandular structures gained general acceptance. Fenwick stated that he lacked the means to "collect and subject to chemical tests the gastric fluid during life," and it remained for Cahn and Von Mehning²⁶ in 1886 to demonstrate definitely the absence of free hydrochloric acid. The occurrence of anacidity has since been widely recognized.²⁷⁻²⁸ In 143 well-documented cases Levine and Ladd²⁹ found achlorhydria so constant that they concluded it was an invariable feature of the disease. However, instances of true Addisonian anemia with normal gastric acidity have been described, but the number of reported cases only serves to emphasize their extreme rarity.¹⁶⁻³⁰⁻³¹ The return of hydrochloric acid following treatment has also been noted.^{32-33,34}

While the anatomical changes offer a plausible explanation for the lack of secretion, the question still remains whether the gastric pathology precedes or is the cause of the anemia, or whether it is merely part of the picture, perhaps entirely secondary to the other aspects of the disease. The early theory²⁰⁻²¹⁻²³⁻²⁴⁻²⁵ was that the anemia depended "on profound degeneration of the gastric tubules" caused possibly by abuse of alcohol,²⁵ which reduced the amount of gastric juice to such an extent that the assimilation of food was inadequate to the wants of the body. Much stress was placed on the presence of anacidity long before the onset of anemia.^{7-20,35,36-37} This point of view received support from reports describing the supervention of a similar anemia following gastrectomy in man.^{37-38-39,40-41} However, it is not yet certain that this is invariably true,⁴² and there is experimental evidence that gastrectomy in dogs is not followed by anemia.⁴³ Neusser⁴⁴ in 1899 offered the alternative view that the gastrointestinal changes were secondary, and in 1900 Strauss⁴⁵ made metabolic studies which revealed no unusual alteration in the utilization of protein or fat in achylia gastrica. Recent studies of Griffiths⁴⁶ and Maltby,⁴⁷ however, indicate that there is deficient digestion of beef protein by the gastric juice of patients with Addisonian anemia. Hurst,⁴⁸ reemphasized the idea of a primary gastrointestinal defect, arguing that hemolytic and neurotoxic factors might be liberated in the intestine as a result of abnormal bacterial activity on proteins incompletely digested in the stomach. He showed that there was an excessive number of bacteria due to absence of the normal antiseptic action of the gastric juice. Davidson⁴⁹

believes that more critical studies of the gastrointestinal bacteriology of Addisonian anemia both before and after treatment fail to support these ideas. In the light of recent developments Hurst has lately modified his theory.⁵⁰

Other macrocytic anemias closely related to true Addisonian anemia are those of sprue, celiac disease, the anemia of Hill, diarrhea, tropical macrocytic anemia of India, and bothrioccephalus anemia. In these diseases there seem to be basic etiologic factors other than parasitism. Achlorhydria is present in many but not all of the cases and the anemia is usually improved by the administration of liver. In certain instances an autolyzed yeast preparation, rich in vitamin B-complex, has been effective.

Older reports noted an anemia with a low color index and small corpuscular diameter^{35, 36} as a frequent complication of achlorhydria. Recently there has been described as a specific entity, under the designation idiopathic hypochromic or microcytic anemia,^{51, 52, 53, 54, 55, 56} an anemia occurring chiefly in middle-aged women and associated with gastric hypoacidity or anacidity, glossitis, and frequently with menorrhagia. In these patients, administration of iron is followed by rapid improvement with increase of hemoglobin and red cells although the low acidity persists.^{56, 57, 58} Bloomfield⁵⁹ believes that since achlorhydria is not a constant feature it should not be assigned a primary rôle in pathogenesis. Dameshek⁵⁴ writes that clinical features as remissions and relapses, sore tongue, gastrointestinal symptoms and paresthesias definitely relate this disease to Addisonian anemia. It is probably dependent, he believes, upon defective gastric secretion associated with achlorhydria, resulting in an inadequate digestion and assimilation of organic iron which leads to faulty hemoglobin synthesis and improper maturation of red cells in the bone marrow. Consistent with this view is the demonstration by sternal biopsy of a hyperplastic marrow crowded with normoblasts and erythroblasts,⁵⁴ the curative effect of large doses of inorganic iron,^{58, 60} and the observation by Mettier and Minot⁶¹ that iron is better absorbed when the gastrointestinal medium is acid than when alkaline. While Addisonian anemia responds to liver therapy and not to iron, and microcytic anemia to iron and not liver, occasionally in each disease both are required to obtain a complete remission. Heath reports the occurrence of both Addisonian anemia and idiopathic microcytic anemia in each of three sisters.⁶²

In pregnancy there occurs a hypochromic type of anemia similar to idiopathic microcytic anemia and relieved by proper doses of iron. In the last third of pregnancy there develops not infrequently a macrocytic anemia which is invariably associated with achlorhydria and responds usually to liver. Spontaneous recovery follows the termination of the pregnancy. This form is indistinguishable from Addisonian anemia, and it also seems to have a definite etiological relationship to deficiency of the gastric secretion.⁶³

PATHOGENESIS OF ADDISONIAN ANEMIA

A The Antianemic Factor

Following the provocative experiments of Whipple and his associates on anemia in dogs,⁶⁴⁻⁶⁵ Minot and Murphy⁶⁶ in 1926 published their important observations on the use of a liver diet in the treatment of Addisonian anemia. The discovery that large amounts of whole liver by mouth induced a rapid and striking improvement,⁶⁷ was followed by the demonstration that a protein-free liver extract containing less than 2 per cent of the original material was equally effective.⁶⁸ Then came the successful results obtained with kidney,⁶⁹ and in 1927 Stugis and Isaacs⁷⁰ announced that whole chopped hog's stomach contained an antianemic factor quite comparable to that in hepatic tissue. Meanwhile Minot, Murphy and Stetson⁷¹ had hypothesized that the response to liver was due to the presence of a specific active principle capable of promoting the growth and maturation of the immature red cells that crowd the bone marrow in the relapse of Addisonian anemia.

Castle and his co-workers sought to correlate the almost constant presence of achylia in the disease with the beneficial effect of liver. The singularly quantitative nature of the response of the patient to therapy suggested the possibility of a deficiency disease. The conception was that gastric digestion failed to elaborate from food the specific antianemic principle present in liver, possibly because lack of acid and pepsin eliminated protein digestion, which is overtly the principal chemical function of the normal stomach. Consistent with this idea was the knowledge that the effective substance in liver extract was probably a nitrogenous base or polypeptide, and so conceivably a derivative of protein.⁷²⁻⁷³

In a series of experiments,¹³⁻¹⁴⁻¹⁵⁻¹⁶ Castle and his associates demonstrated the primary rôle of the gastric disorder in the pathogenesis of the disease. They showed that typical remissions, similar to those produced by liver, could be induced by the daily administration of 200 grams of raw beef muscle previously digested by normal gastric juice, either in the stomach or in vitro. Neither the beef nor the gastric juice was effective alone, nor were the two when fed separately. Moreover hydrochloric acid, pepsin, and rennin were eliminated from consideration by means of similar experiments. In conclusion Castle postulated Addisonian anemia to be a deficiency disease of a new type caused by lack of a substance produced from protein during the course of normal digestion which the defective gastric juice of Addisonian anemia was incapable of elaborating. In the healthy person an *intrinsic factor* is secreted by the gastric mucosa. It is organic in nature, thermolabile, neither acid, pepsin nor rennin but possibly an enzyme. This reacts with an *extrinsic factor* derived from the diet, present in beef muscle and protein in nature, to form a heat stable antianemic principle which is absorbed and stored in the liver, kidney, and possibly to a lesser extent in all tissues. The remissions following the use of liver and kidney

in Addisonian anemia are explained by assuming the presence of this stored antianemic substance. As a result of atrophic and chronic inflammatory changes, the stomach of the individual with Addisonian anemia does not secrete the intrinsic factor. Isaacs and Goldhamer⁷⁴ suggested that the difference between normal gastric juice and that of Addisonian anemia might be quantitative rather than absolute. Repeating Castle's experiment, they fed to a patient with Addisonian anemia beef incubated with 1500 c c of gastric juice collected from five patients with the anemia, and obtained a moderate reticulocyte response.

Previously Castle¹⁶ had reported two patients in whom blood pictures of Addisonian anemia occurred in the presence of apparently normal gastric contents, but in which the presence of the intrinsic factor could not be shown. Moreover the presence of the "intrinsic" factor was demonstrated in an individual with achylia gastrica but without anemia, and in three patients with hypochromic anemia who responded to iron but not to liver therapy. A contrary observation was that of Barnett⁷⁵ who reported two patients with long-standing anacidity in whose gastric secretions, despite the absence of any anemia, no evidence of intrinsic substance could be found. Barnett⁸⁰ also described a patient with otherwise typical Addisonian anemia who possessed gastric juice normal in volume, appearance and acidity and high in content of the intrinsic factor. Castle⁷⁶ has recently modified his theory to include such conflicting cases as the latter by assuming that the defect may lie in inadequate absorption of the antianemic substance even if elaborated in adequate amounts. Another link in the chain was added by the work of three groups of investigators,^{77, 78, 79} who showed independently that the livers of normal and adequately treated patients with Addisonian anemia contained the antianemic principle, whereas it was absent from the livers of untreated or inadequately treated cases. These observations, then, bear witness to the idea, previously broached, that the factor of storage plays a rôle in hematopoiesis. Furthermore an explanation of the mechanism of the macrocytic anemia which often occurs in cirrhosis of the liver is suggested, and Goldhamer et al^{79, 80} have brought experimental evidence to bear on this point.

Cohn, Minot et al^{68, 72, 73} have analyzed the nature of the potent material in liver. Eliminating from raw minced liver the proteins precipitated at pH 5 and those heat coagulable, and removing all ether and alcohol-soluble extractives, they obtained an alcohol precipitate, extractive G, which contained the active substance. This was thermostable, neither protein, carbohydrate nor fat in nature, and apparently not a vitamin. Judging from its nitrogen content it seemed to be either a nitrogenous base or a polypeptide. Liver Extract 343 N N R is essentially the fraction G of Cohn.

Potent extracts of liver have proved satisfactory when given by mouth^{71, 81} and also when administered parenterally^{82, 83, 84, 85, 86, 87}. Orally about nine grams of extract, derived from an equivalent to 300 grams of whole liver, has proved the minimal daily amount which can produce a maxi-

imum reticulocyte response in the relapse phase of the disease^{81, 88} An intense blood crisis may result with a single massive dose of the extract, with striking immediate clinical effects, but the duration is not prolonged⁸⁹ When administered parenterally extracts derived from significantly smaller amounts of liver are effective^{90, 91} and the cost of treatment is thereby reduced In addition, the treatment can be controlled more effectively, and the disturbing variable of intestinal absorption circumvented Isaacs, Sturgis et al.⁹² have recently prepared a product for intravenous administration by treating the extract with acetone after filtering through permutite An injection of material derived from 125 grams of liver produced an average maximum reticulocytosis higher than that reached after about 40 times as much material taken by mouth in divided daily doses

Another thread was woven into the story of liver when Reimann⁹³ found a marked increase in potency of material digested in normal human gastric juice Walden and Clowes⁹⁴ produced a very active preparation by the interaction of liver with small amounts of fresh hog gastric tissue Fouts and Zervas corroborated this finding using the product called extralin⁹⁵ Later Helmer, Fouts and Zervas⁹⁶ repeated their experience by incubating subminimal quantities of the extract with normal gastric juice Finally Herron and McElroy⁹⁷ accomplished the same potentiation of liver without gastric juice by the simple process of allowing the liver to stand at warm temperatures and permitting autolysis to take place In 13 cases they found that the oral dose of autolyzed liver approached the intramuscular requirements of other preparations They ventured the hypothesis that this increase in potency was due to hydrolysis of the nucleoproteins of the liver by the autolytic enzymes which are present in every cell as well as the stomach, but which differ from the proteolytic enzymes, pepsin and trypsin, in that the latter only slightly affect nucleoproteins⁹⁸ In a similar series of patients we have been able to verify the fact that autolyzed liver has an enhanced potency but we are not prepared to go as far as McElroy and Herron in comparing it with parenteral dosage

The development of the concept of an antianemic factor formed by the interaction of an intrinsic and an extrinsic principle, took an unexpected turn when Morris and his co-workers found that the single injection of normal, concentrated, neutralized gastric juice produced an intense and prolonged reticulocyte response and remission in patients with Addisonian anemia^{17, 18, 19, 99} In two classical cases¹⁰⁰ the single intramuscular injection of five and eight cubic centimeters of material equivalent to 3200 and 5700 c c, respectively, of native swine gastric juice produced a marked reticulocytosis of 34 and 44 days' duration followed by a rapid increase in hemoglobin and red cells The active principle was demonstrated in the gastric juice of man, swine and dogs, and found to be heat labile, dialyzable through a collodion sac, presumably exhaustible, and able to withstand chemical treatment known to destroy enzymes^{17, 18, 19} It was tentatively considered to be in the nature of a hormone normally secreted internally by the stomach, and

designated *Addison* by them. Conner¹⁰¹ confirmed the findings of Morris by injecting normal concentrated human gastric juice into one patient with Addisonian anemia. Wilkinson,¹⁰² however, reported negative results but he neutralized the human gastric juice previous to vacuum distillation, a procedure which apparently inactivates the hematopoietic substance. One of the authors (S. K.) was able to demonstrate a hemopoietic substance in the concentrated gastric juice of dogs when injected into rabbits. Fouts, Helmer, and Zerfas¹⁰³ took up these studies and found that fresh normal human gastric juice concentrated at ice box temperatures by ultrafiltration in about 48 hours was inactive on intramuscular injection in patients with Addisonian anemia. When, however, this inactive material was diluted with water, and then reconcentrated by vacuum distillation at 40° C it proved very potent. Moreover, while fresh juice was inactive, storage of the secretion on ice for two months, and then concentration by ultrafiltration yielded a material which was entirely effective. Apparently before the gastric juice becomes potent, a chemical reaction must take place, which proceeds rapidly at temperatures around 40° C, slowly at ice box temperatures, and not at all above 60° C.

These reports concerning the effects of injected gastric juice came as disturbing elements into an otherwise perfect picture. The obvious explanation, to reconcile them with Castle's concepts, was that the inspissated gastric juice was merely a concentrate of the intrinsic factor which interacted with the extrinsic factor of muscle protein at the site of injection. When investigation¹⁰³ failed to reveal evidence of necrosis or pathological change at the site of injection, it was suggested that the interaction might occur at some more remote point. To this argument there was no direct answer but if it were true, then gastric juice concentrated by ultrafiltration and shown to contain the intrinsic factor should be equally effective, which Fouts, Helmer and Zerfas¹⁰³ pointed out was not the case. Finally, Minot¹⁰⁴ noted that fever, chills and malaise accompanied the injection of gastric juice^{99, 100, 101} and that the sustained reticulocyte response was suggestive of a toxic effect similar to that occasionally seen following injections of arsenic formerly used in the treatment of pernicious anemia. However, Morris and his associates¹⁰⁰ have been able to eliminate all untoward reactions by means of an acetone extract of gastric fluid, and it had previously been shown by others^{102, 103} that the same systemic reactions occurred following injections of gastric juice which failed to stimulate the bone marrow. Fouts, Helmer, and Zerfas¹⁰³ have come to the conclusion that gastric juice contains both the intrinsic and extrinsic factors which interact to form a hemopoietic agent during the process of vacuum distillation at 40° C. We are inclined towards this explanation and to suggest that the extrinsic factor present is derived either from the protein of gastric mucin or cellular debris, a point which awaits experimental trial.

There is evidence that the injection of concentrated gastric juice causes an increase in leukocytes as well as erythrocytes.¹⁰ According to Morris¹⁰

the factor in gastric juice which stimulates reticulocytosis is thermolabile whereas the polymorphonuclear leukocytosis is induced by a thermostable principle. Using canine gastric juice, injected into rabbits under controlled conditions, one of us (S. K.) has been able to induce a similar leukocyte and reticulocyte response, but a separation of two principles by means of heat could not be accomplished.

Morris and his associates¹⁰⁶ have suggested the possibility that erythremia might be due to an excess of the hematopoietic principle in gastric juice which they believe is a hormone and have called Addisin. A patient with erythremia was subjected to gastric lavage over a period of six months, during which time the number of red blood cells decreased from 10,000,000 per cu mm to 5,300,000 and subsequently returned to the former level when lavage was discontinued. This was attributed to the mechanical withdrawal of Addisin. The implications of these ideas stimulate the imagination, and it is hoped that they will likewise stimulate further research to test their validity.

B Vitamin B

The literature records only a few investigations of the influence on gastric secretion of a dietary regime deficient in the vitamin B-complex. Moreover interpretation of these is unsatisfactory because of the complex nature of vitamin B and because the unequivocal production of either vitamin B₁ or B₂ (G) deficiency has not in most instances been established.¹⁰⁷ Danysz and Koskowski¹⁰⁸ and Fainum¹⁰⁹ reported a marked decrease in both volume and acidity of secretion, the former in pigeons fed on a ration of polished rice and the latter in Pavlov pouch dogs who received a diet autoclaved in alkaline medium to destroy the antineuritic factor. Cowgill and Gilman¹¹⁰ observed the development of gastric achlorhydria in dogs that were given rations lacking vitamin B-complex. Complete anacidity was produced by Webster and Armour under absolute avitaminosis in dogs without the exhibition of anorexia or inanition.^{111, 112} Gastric secretion was restored by autoclaved and by powdered yeast, and lost when these were withdrawn. The authors believed that the vitamins contained in yeast were absolutely essential to the normal secretory activity of the gastric mucosa. Recently Miller and Rhoades¹¹³ produced in dogs a syndrome similar to clinical sprue, with feedings deficient in vitamin B₂ by a modification of the Goldberger black tongue producing diet. There were glossitis, anorexia, vomiting, striking diarrhea and loss of weight. The blood changes were marked, and microscopic studies of the bone marrow revealed pictures virtually indistinguishable from those of sprue. No studies on gastric secretion were reported.

Some evidence has been advanced that deficiency in vitamin B-complex, and especially of the B₂ factor, may be responsible for the atrophic glossitis which is frequently associated with achlorhydria and anemia. Very significant from a clinical viewpoint is the obvious parallelism between pellagra,

sprue, and Addisonian anemia in their common glossitic and gastrointestinal manifestations,¹¹⁴ and the frequent occurrence of anacidity in pellagra. That glossitis may be present with normal gastric secretion, however, is shown in certain cases of sprue and idiopathic microcytic anemia. Lewis¹¹⁵ believes the smooth tongue in all probability represents a deficiency manifestation. In a patient with sprue he observed that absence of the intrinsic factor occurred in the presence of a normal tongue. With a diet deficient in vitamin B-complex Hutter and Middleton¹¹⁶ produced smooth tongue in rats. A high vitamin B-complex ration given by them to three patients with Addisonian anemia and glossitis resulted in the clearing up of the glossitis in only one, without affecting the blood picture. In the other two the glossitis improved when a low vitamin B-complex diet and liver were subsequently given. The question was raised as to whether smooth tongue may not be a conditioned deficiency in which the absorption and assimilation of the lower vitamin intake may be rendered more adequate by liver extract. That the parenteral administration of liver extract alone clears up glossitis is significant when one recalls that liver and liver extract are themselves rich in vitamins B₁ and B₂.^{117, 118, 119, 120}

In the meantime Wills¹²¹ in India reported cases of tropical macrocytic anemia, similar to Addison's anemia though with or without achlorhydria, cured by an autolyzed yeast product, marmite, rich in vitamin B₂. This substance was found to equal liver extract in its efficacy.¹²² It was subsequently used successfully in treating celiac disease with a macrocytic anemia and free gastric acidity,¹²² in cases of sprue¹²³ and apparently in certain cases of true Addisonian anemia.^{124, 125, 126} Connery and Goldwater¹²⁷ obtained a typical reticulocyte response in two of four patients with classical Addisonian anemia by the oral administration of vitamin B-complex alone. Russell¹²⁸ gave small doses of brewer's yeast to four cases of true Addisonian anemia and obtained slight increases in the number of reticulocytes. The subsequent administration of liver extract parenterally was followed by a greater reticulocytosis and characteristic remission. Lassen and Lassen¹²⁹ tested various yeast preparations on eight patients with Addisonian anemia and concluded that yeast was without antianemic effect or possibly it contained minimal amounts of the antianemic factor. Cohn et al.^{68, 72} reported essentially negative results in treatment by the feeding of 120 grams of yeast cake daily and with various concentrates of vitamin B. Strauss and Castle¹¹⁹ and Davidson¹³⁰ found autolyzed yeast alone inert.

Strauss and Castle considered the possibility that marmite might contain the extrinsic factor which they believed interacted with the intrinsic factor present in normal human gastric juice to form the hematopoietic substance.¹¹⁹ On using an autolyzed yeast preparation similar to marmite called Vegex incubated with normal gastric juice, or Vegex after autoclaving for five hours to destroy vitamin B₁ or an 80 per cent alcoholic extract of the preparation, it was found that in doses equivalent to 12 grams of marmite, each of these mixtures produced typical reticulocyte crises and remissions in Addi-

sonian anemia They concluded that the extrinsic factor was a substance closely related to vitamin B₂, if not vitamin B₂ itself The suggestion was made that the cases of sprue, tropical macrocytic anemia and celiac disease which had responded to the administration of yeast, had been due to lack of the extrinsic factor, and that the intrinsic factor has been present in the gastric juice Consistent with this hypothesis was the observation that the protein extract of washed beef muscle originally used by Castle as a source of the extrinsic factor, was rich in vitamin B₂⁸⁷ as are also commercial liver extracts and stomach preparations^{117, 118, 119, 120} Since Liver Extract 343 is rich in vitamin B₂,¹²⁰ the potentiation of this extract with hog stomach by Walden and Clowes was readily explained

Wills,¹³² however, believed that the use by Strauss and Castle of 80 per cent alcohol would inactivate or destroy vitamin B₂ as has been stated by Chick and Copping¹³³ She found that dried brewer's yeast and a watery yeast extract, both rich in vitamin B₂, and egg white containing doses of the principle seven times that of marmite, all failed to produce results in patients with tropical macrocytic anemia who then responded excellently to marmite While dried brewer's yeast was without effect, marmite, which is an autolyzed extract made from brewer's yeast, was specifically curative The responsible factor was heat stable and alcohol soluble She concluded that autolysis broke down some of the protein into simpler products and that the marmite probably owed its properties to one of these Subsequently, Wills and Naish¹³⁴ treated a classical case of Addisonian anemia with vitamin B₂ from egg white Both egg white alone, and egg white incubated with normal gastric juice given daily were without effect, following which the patient received by mouth the equivalent of one pound of liver daily with excellent result They believed that the extrinsic factor was not vitamin B₂, but some other substance present in both animal protein and marmite To this point of view Castle has recently subscribed¹³⁵

COMMENT

The development of thought on the relationship of gastric secretion and hematopoiesis has taken place with amazing rapidity Not only have important advances in the understanding and treatment of disease been made but new and equally significant contributions to fundamental physiology as well have been added A brief summary of what has been learned may be stated as follows

The dependence of hematopoiesis upon normal gastric function has been established While gross disturbances in the chemical composition of gastric secretion may play a rôle in the pathogenesis of certain microcytic hypochromic anemias, the development of Addisonian and related macrocytic anemias is conditioned not upon these gross disturbances but upon one or more of the following

- (a) Diminution or absence of a substance in gastric secretion, an intrinsic factor

- (b) Reduced oral intake of a substance derived from certain protein foods, the extrinsic factor
- (c) Deficient absorption of an antianemic substance formed by the interaction in vivo and vitro of the intrinsic and extrinsic factors
- (d) Impaired storage of the antianemic substance principally in the liver

The intrinsic factor has been shown to be organic in nature, thermolabile, neither acid, pepsin nor rennin but probably an enzyme. The extrinsic factor is found in certain but not all meats and autolyzed yeast. Its presence in casein and gluten could not be demonstrated. Its identity as vitamin B₁₂ has been disproved, and certain assays of nucleoproteins and nucleic acid have failed to reveal it. The antianemic principle is thermostable, and has been identified as a nitrogenous base or polypeptide. It is found in the livers of normal individuals or patients with Addisonian anemia adequately treated, and absent from the livers of patients in relapse or inadequately treated. It has been found in animal livers and kidneys and desiccated hog's stomach. The injection of normal gastric juice concentrated by vacuum distillation results in a prolonged reticulocytosis and remission of Addisonian anemia. When substances containing the antianemic principle are subjected to (a) interaction with gastric juice, (b) interaction with gastric tissue, or (c) autolysis, an unexplained increase in antianemic potency is effected.

Although the contributions that have been made fit into an orderly mosaic, the outline and dimensions of which have been fairly well defined, there are still many large gaps in the pattern. One of the most important of these is the determination of the exact nature of Castle's intrinsic factor. If it is an enzyme its properties, actions, source, and relation to the autolytic enzymes in tissue cells await elucidation. The explanation of the conflicting results when nucleoproteins were used as the source of the extrinsic factor may throw some light on the nature of this factor and its relation to nucleoproteins. The mechanism of the action of injected concentrated gastric juice is still obscure and attempts to reconcile it with Castle's ideas are not altogether convincing.

A further study of gastric function and of the dietary of herbivora, especially in regard to the extrinsic factor, seems warranted. The consistent failure to produce a macrocytic anemia in animals by gastrectomy suggests that in these the duodenum or some other portion of the gastrointestinal tract may be concerned in the elaboration of the intrinsic factor. Finally there is a vital need for a simpler and more easily controllable method for assaying the antianemic principle. The awakening of widespread interest in the recognition and treatment of pernicious anemia has resulted in a sharp decline in the number of patients that are referred to those who are studying the disease, and progress seems to stand in its own way. But this is not a new problem in medical research.

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TREATMENT OF LOBAR PNEUMONIA BY ARTIFICIAL PNEUMOTHORAX *

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LOBAR pneumonia may be considered to be an infectious (usually pneumococcic) lobar atelectasis of the lung. The work of Coryllos and Bimbaum¹ and others has strengthened this conception of the disease. The

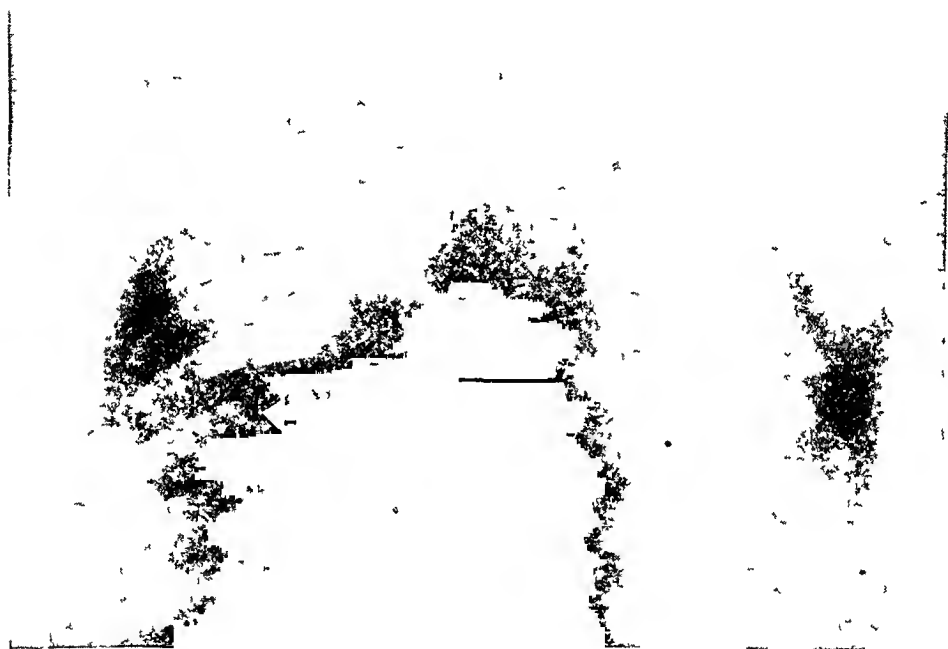


FIG 1 Case 7 Male, age 17 Took a cold on 3/7/34 Entered the hospital on 3/9/34 with temperature of 101.4°, pulse 110, respiration 28 Film on 3/12/34 corresponds with clinical findings of left lower lobar consolidation

pneumococcic infection of the bronchus causes the formation of a very tenacious fibrin-containing sputum which may readily narrow or completely occlude a large bronchus. With the occlusion of the main bronchus to a lobe, lobar atelectasis takes place, beginning at the periphery where the greatest number of alveoli are found, and progressing toward the hilus, while there follows a pneumococcic cellulitis proceeding peripherally from the hilus abetted by the negative pressure in the atelectatic area. Physical

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findings early in pneumonia would seem to substantiate this theory, as we frequently find the breath sounds diminished early in the disease with no definite signs of consolidation. Several roentgen-rays in our series demonstrate a condition which would seem to be best explained in this way. The toxic symptoms caused by the spread of the infection become more acute as the lung goes through the stage of red hepatization. If it happens that the occlusion of the bronchus is relieved early in the process, from the second to the fourth day, the disease takes an abortive form with an early crisis. The usual freeing of the occlusion occurs between the fifth and the eighth days with crisis, followed by more or less clearing of the lobe of its inflammatory



FIG 2 Case 7. Arrows point out lung margins after introduction of 900 cc of air. Film shows partial consolidation of left lower lobe and some involvement of upper lobe. Crisis occurred 44 hours after initial pneumothorax treatment.

exudate, and leaving little subsequent damage. If relief of the obstruction of the bronchus is long delayed, then greater and greater changes in the lung parenchyma and bronchi take place—resulting in unresolved pneumonia, lung abscess or bronchiectasis. In accordance with this theory, clearing of the plugged bronchus precipitates the crisis and if this can be accomplished early, before all the smaller bronchi become tightly plugged, the severity of the illness may be aborted.

The very beneficial effect of artificial pneumothorax in massive atelectasis in tuberculosis has long been observed. The close similarity between

this condition and lobar pneumonia would indicate that perhaps equally good results might be obtained by this treatment in pneumonia. By collapsing a lung, it may be possible to free the mucous plug, thereby inducing an earlier crisis. Perhaps by lessening the negative pressure the spread of infection out from the hilus may be retarded. Accompanying the local diminution of blood volume incident to the pneumothorax it is reasonable to

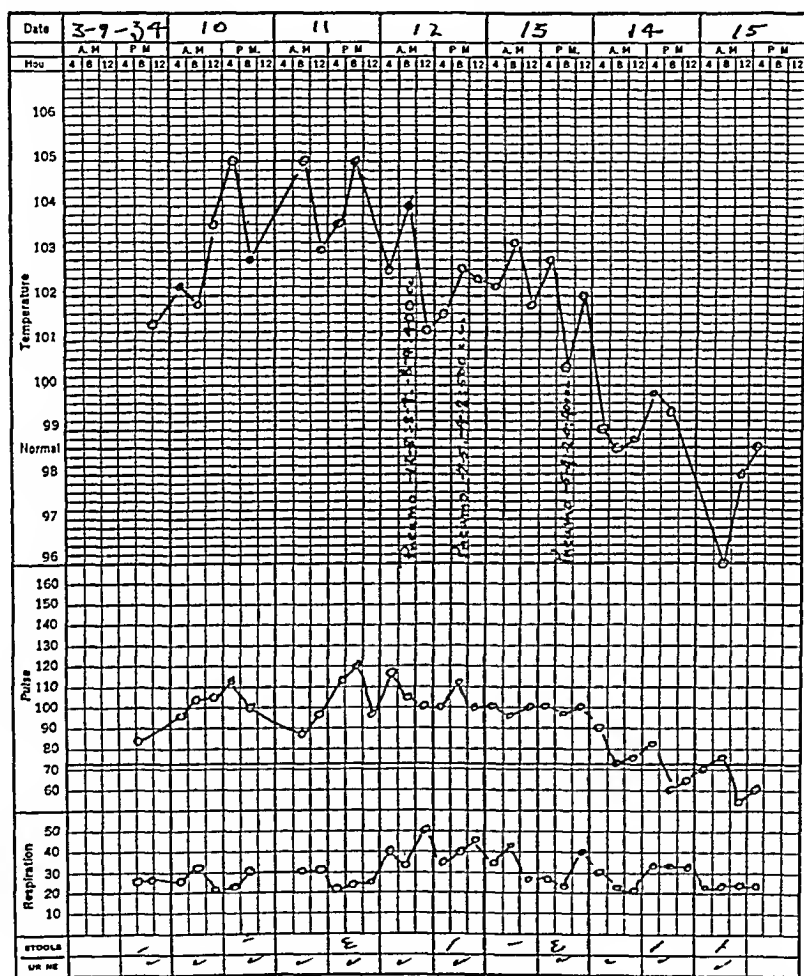


FIG 3 Case 7 Temperature chart of severe pneumonia with delirium and severe pain in the left side, three days duration. Pneumothorax — 12—8 —8—4 400 cc. Patient continued delirious and after 12 hours a second treatment was given, —7—5 —4—2 500 cc. Previous severe pain relieved. General condition still not good, 24 hours later, —5—4 —2—0 400 cc. Temperature reached normal eight hours after this treatment. Total duration of high temperature four and three-quarter days. Critically sick pneumonia case given three pneumothorax treatments with uncomplicated recovery.

suppose that there will be a reduction in the absorption of toxins and bacteria into the circulation. On these theoretical considerations is based the rationale of the treatment.

Friedemann² in 1921 reported a series of nine cases treated with pneumothorax with no deaths. His conclusions were sufficiently favorable to encourage further study. Nothing further is reported until the work of Ibrahim and Duken³ who in 1928 published a report of three cases and felt that the treatment had merit. Klotz⁴ in 1928 reported several cases where pneumothorax was attempted but he was exceedingly skeptical as to its value. Coghlan⁵ in 1932 reported six cases treated by pneumothorax and recommended the treatment very highly. Perlroth and Topercer⁶ in the same year disagreed with practically all of Coghlan's conclusions and advised against the use of pneumothorax in pneumonia. Moorman⁷ in a recent

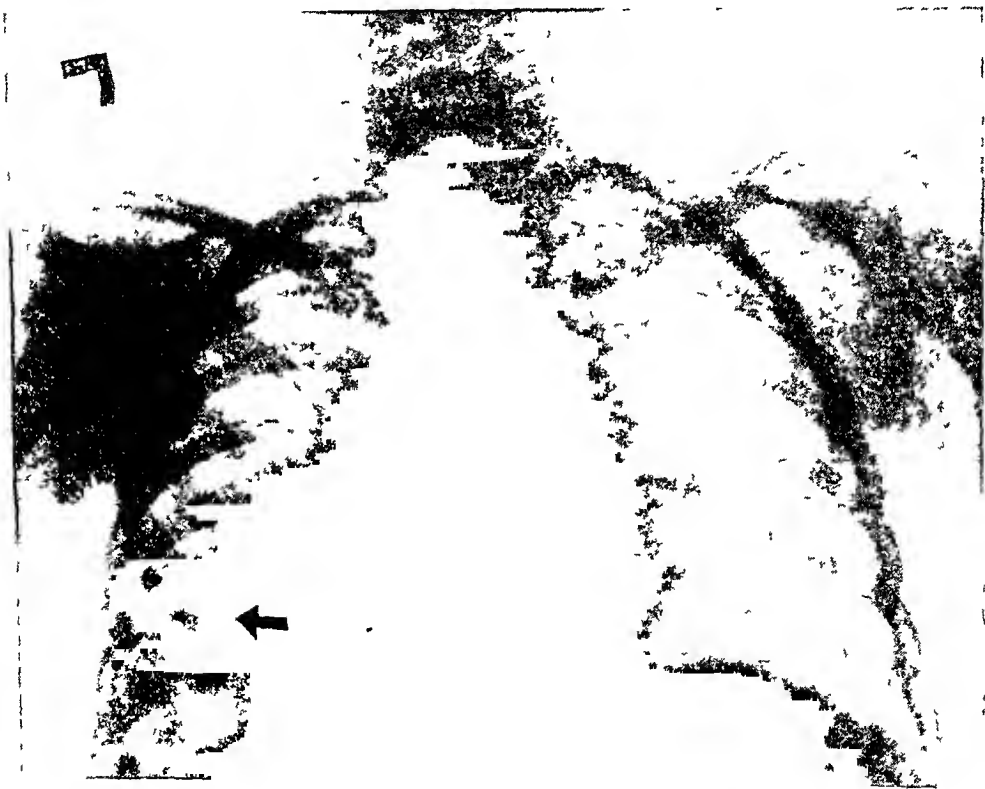


FIG 4 Case 15 Arrow points to lower lobe consolidation, acute pneumonic process

article reviews the literature and his own experience in this work and recommends its further use.

Behrend and Cowper recently reviewed the literature and reported 11 cases of lobar pneumonia with no deaths from pneumonia and two deaths from causes unrelated to the pneumothorax, one "an overwhelming septicemia," the other a "pneumococcic meningitis" occurring on the twenty-first day of the disease.

This paper presents our results with pneumothorax in 18 cases treated between January and April 1934.

In the accompanying chart our treated cases are grouped into adults and children with the dividing line at 12 years. The oldest person given pneumothorax was 36 years, the youngest three. There were eight adults and 10 children. Under associated diseases it is indicated whether these conditions were previously existing or were complications.

The days given as duration of pneumonic symptoms indicate the time before artificial pneumothorax was instituted. Usually pneumothorax was done promptly after the patient was seen by us, but occasionally a period of observation was necessary for definite diagnosis. Often it was very difficult to judge just when the pneumonic symptoms began, but usually high



FIG 5 Case 15 Pneumothorax established. No adhesions. Consolidation still present in collapsed lung.

temperature, chill and pain in the chest ushered in the pneumonia from a preexisting respiratory infection.

Each case was proved to be lobar pneumonia by roentgen-ray, physical examination and clinical picture. Roentgenograms were taken before and after collapse was instituted, just before discharge from the hospital and, in many cases, another observation by fluoroscope or a roentgen-ray was taken about three weeks after discharge. The side involved seemed of no consequence, as the cases were equally divided between the two sides with equally good results. An estimate indicating the clinical severity from one

days were taken after pneumothorax. Only those patients in whom air was actually injected are included. There were two other patients in whom the lung was completely adherent. No air could be injected and these cases are not included in this report.

All patients complained of more or less pain in the affected side. In some there was a temporary increase after pneumothorax but it was always of brief duration. Cases marked with one plus indicate complete relief of moderate pain or moderate relief of severe pain, while two plus indicates a striking relief of severe pain.

In the first two charts, under the heading "pressures and amounts in c c," the first two numbers indicate the pressures before, and the last two numbers after injection. The figures are centimeters in the water manometer reading up or down from the neutral in one leg only. The time between injections is given in hours.

Under "fluid" is listed tea-colored fluid which remained sterile in two cases, while in the next column are listed the cases which went on to pus formation. Sterile fluid cases required no treatment and the presence of such fluid in no way affected convalescence.

The time from the original pneumothorax until the temperature became practically normal is listed. It might have been slightly elevated after that but the crisis had passed and that was the essential factor. The total duration of high temperature before the initial pneumothorax plus that afterward gives an idea of the duration of the disease when treated by this method and makes possible a comparison with the duration of pneumonia when untreated, or when treated in some other manner.

CASE REPORTS

Case 1 W. C., well developed, well nourished, previously healthy male laborer, 20 years old. A cold for one week terminating in right-sided pneumonia of four days' duration, with severe pain. Sputum rusty—Type IV. Temp 102.4°. Pulse 126. Resp 32. Attempt at pneumothorax in posterior axillary line failed but a free space was found in front. Readings —4—3 before and —3—2 after injection of 300 cc of air. Marked relief from pain, and improvement in all symptoms. Eighteen hours later a second injection was given, —3½—1 —1+2, 300 cc. There were quite marked adhesions but clinical results were excellent and temperature returned to practically normal in eight hours after first injection, making a total of four and one-third days pneumonia. It is perfectly possible that the second pneumothorax treatment was unnecessary.

Case 2 R. T., poorly developed and nourished male laborer. Had been somewhat asthmatic all his life—although not recently severe. Bronchitis for two weeks terminating in left-sided pneumonia three days before. Temp 102.4°. Pulse 130. Resp 36. Asthmatic symptoms, increased by pneumonia, somewhat alleviated by adrenalin. Pneumothorax, —7—3 —5—2, 400 cc. Relief of sore spot in left chest. Temperature practically normal next day and in spite of doubtful necessity second injection was given, —9—2 —2+1, 350 cc. Such a marked change in pressure after a small amount of air injected suggested diffuse adhesion of lung. Uneventful recovery of a moderately severe pneumonia in an asthmatic in four days.

Case 3 C. M., well developed, well nourished laborer 35 years old. Respiratory

CHART I—Continued

| No Age Type | Past History | Ass Diseases | Clin Sever ity | Days Sick Before Pn | Hrs Fever After Pn | Temp Pulse Resp | Side Adhe sions | Relief of Pain | Pressures and Amounts in c c | Fluid Pus | Results |
|-------------------|--|-------------------------------|----------------------|------------------------------|-----------------------------|-----------------------|-----------------------|----------------------|---|------------------|---------|
| Adult Cases | | | | | | | | | | | |
| No 5 32 III | Pneumonia in child hood Healthy | Acute hem nephri tis | ++ | 1 | 78 | 103° 126 40 | Right +- | ++ | -4-3, -3-2 400 24 hrs -5-3, -3-2 450 24 hrs -3½-1, -1½-½ 400 30 hrs -4-2, -2½-1 400 | Fluid Sterile | Good |
| No 6 2½ | Healthy | Double otitis media | + | 4 | 24 | 101° 100 38 | Left +- | + | -8-7, -7-5 700 | Fluid Sterile | Good |
| No 7 17 | Healthy | | +++ | 5 | 44 | 104° 118 40 | Left 0 | ++ | -12-8, -8-4 400 12 hrs -7-5, -4-2 500 24 hrs -5-4 -2-0 400 | | Good |
| No 8 36 IV | Healthy | Otitis media | ++ | 1 | 12 | 104.4° 120 40 | Right 0 | + | -6-3, -5-2 700 | | Good |

CHART II

| No | Age | Type | Past History | Ass Diseases | Clin Severity | Days Sick Before Pnx | Hts Fever After Pnx | Temp Pulse Resp | Side Adhesions | Relief of Pain | Pressures and Amounts | Fluid Pus | Results |
|-----------------|-----|------|----------------------|--------------|---------------|----------------------|---------------------|---------------------|----------------|----------------|---|-----------------------|------------------|
| Childhood Cases | | | | | | | | | | | | | |
| No 9 | 12 | | Pneumonia 3 times | Otitis media | + | 4 | 168 | 103° 110 40 | Left — | None | -4-3, -3-2 24 hrs -3-1, -2-1 250 | Fluid Spontaneous Pus | Empyema Recovery |
| No 10 | 10 | | Pneumonia and asthma | Asthma | ++ | 4 | 120 | 102.4° 138 36 | Right + | + | -4-3, -3-2 24 hrs -3+1, -2+2 200 Stopped because of asthma | | Good |
| No 11 | 11 | | Healthy | | ++++ | 4½ | 96 | 104.4° 133 32 | Right + | + but returned | -4-3, -2-1 24 hrs 300 -3-2, -1-0 350 -3-1, -1+2 24 hrs 300 -2-1, -0+1 48 hrs 300 8 days sterile fluid | Fluid Spontaneous Pus | Empyema Recovery |
| No 12 | 5 | | Healthy | | + | 4 | 60 | 103.4° 130 48 | Left 0 | + | -4-2, -2-1 18 hrs 250 -2-1, -1-1 175 | | Good |

"Pnx," abbreviation for Pneumothorax

The average duration of pneumonia symptoms before pneumothorax was 4.7 days. Average total high temperature before and after pneumothorax 6.6 days, 60 per cent good results, recovery but with complications 20 per cent, 20 per cent mortality

CHART II—Continued

| No. Age Type | Past History | Ass. Diseases | Clin. Sever- ity | Days Sick Before Pnx | Irr. Ever After Pnx | Temp. Pulse Resp | Side Adhe- sions | Relief of Pain | Pressures and Amounts | Fluid Pus | Results |
|---------------------|---------------------------|---------------------|------------------------|-------------------------------|------------------------------|------------------------|------------------------|----------------------|---|--|------------------|
| Childhood Cases | | | | | | | | | | | |
| No. 13 8 | Healthy | | + | 3 | 32 | 103 6° 102 42 | Right — | ++ | -4-2, -2-1 250 20 hrs -3-2, -2-1 300 | | Good |
| No. 14 6 | Healthy | | ++ | 4 | 56 | 105° 128 32 | Left — | + | -4-3 -2½-1 225 20 hrs -3½-2, -1½-1 225 24 hrs -2-½ -1-0 250 | | Good |
| No. 15 6 | Healthy | | ++ | 5 | 18 | 105° 130 42 | Left — | ++ | -4-3 -2½-1 225 18 hrs -4½-2, -2-½ 250 | | Good |
| No. 16 3 | Healthy | Buccal infection | ++++ | 4 | Not im- proved | | Left ++ | + but returned | ?, +1+2 125 48 hrs ?, +1+2 100 | Fluid Pus | Empyema Death |
| No. 17 11 III | Healthy | Otitis media | +++ | 8 | Not im- proved | 103 2° 130 46 | Right ++ | None | ?, +1+3 200 48 hrs -1+1, +6+7 150 | Fluid Spontaneous Pus Fistula | Empyema Death |
| No. 18 12 | Double otitis media | | +++ | 7 | 14 | 102° 120 40 | Right + | + | -4-2, -2-3 175 | | Good |

infection for one or two weeks developing into right-sided severe pneumonia five days before pneumothorax Temp 102.4° Pulse 110 Resp 34 Sputum Type II Lung adherent in front but free space found behind The first reading was questionable —2½—1½, 350 cc followed by improvement Eighteen hours later, —3½—2—1—½, 400 cc In 24 hours the patient felt better, respirations were faster and the temperature was 103.2° Third injection, —2½—½—1—½, 450 cc Apparently he was embarrassed by this amount of air and the respiratory rate went up to 60 However, it dropped to normal in 18 hours and he was on the road to recovery Total of seven and one-half days fever in a very ill man with three pneumothorax treatments

Case 4 W D, husky laborer, 20 years old, who had had a cold for about two weeks Pneumonia for five days on left side with slight changes on the right side Moderate pain Temp 103.4° Pulse 105 Resp 34 Sputum Type IV Pneumothorax, —5—4—3½—2½, 400 cc In 18 hours the temperature was normal and all symptoms had practically abated Probably an unnecessary second injection was given, —4—2—3—2, 450 cc Rather severe pneumonia with recovery in five and one-half days

Case 5 E G, well developed, well nourished clerk, 32 years old Pneumonia in childhood but healthy as an adult Epidemic of colds in his family with otitis media in two of family at the time of onset At first no chest symptoms but acute nephritis with albumin and blood for five days, followed by well marked right-sided pneumonia of one day duration Severe pain and cough, sputum Type III Temp 103° Pulse 126 Resp 40 Pneumothorax, —4—3—3—2, 400 cc Pain was much relieved and 24 hours later, —5—3—3—2, 450 cc The urinary symptoms were increasing, ankles showed pitting, blood pressure became higher and non-protein-nitrogen was found to be 132 mg Temperature remained high Twenty-four hours later, —3½—1—1½—½, 400 cc Chest signs improved Thirty hours later, —4—2—2½—1, 400 cc Temperature dropped to normal and all symptoms except those relating to the urinary tract disappeared Fluoroscopic examination showed a small amount of fluid in the pleural space In spite of appropriate treatment starting before entrance to hospital the non-protein-nitrogen increased to 200 mg This gradually receded and the patient is now free of symptoms A case of severe Type III pneumonia, coincident with a severe acute nephritis, controlled by four pneumothorax treatments The total duration of fever was five days This would seem more favorable than was to be expected, as the patient went on to complete recovery with lung reexpansion

Case 6 C J, well developed, well nourished male school teacher, 24 years old Respiratory infection and otitis media for several days followed by a moderately severe left-sided pneumonia for four days Roentgen-rays also showed slight shadows on right with consolidation of left lower lobe Temp 101° Pulse 100 Resp 38 On inducing pneumothorax two cc of sterile blood-tinged fluid were removed The pressures were —8—6—7—5, 700 cc Pain, quite severe before collapse, was much relieved Temperature was lowered following pneumothorax, then assumed a low grade septic curve which was believed due to double draining otitis media, the chest symptoms having greatly abated

Case 7 J H, healthy male school boy, 17 years old Left-sided pneumonia for five days Condition very bad with a temperature of 104°–105° even with liberal use of aspirin Temp 104° Pulse 118 Resp 40 Pneumothorax, —12—8—8—4, 400 cc Condition continued delirious and after 12 hours a second injection was given, —7—5—4—2, 500 cc The previous severe pain was relieved, but his condition remained unfavorable Twenty-four hours later, —5—4—2—0, 400 cc The temperature became normal eight hours after this treatment High fever for six and three-quarter days in a critically sick patient who made an uncomplicated recovery after three pneumothorax treatments

Case 8 R D, well developed, well nourished, healthy laborer, 32 years old. There was a moderately severe right-sided pneumonia of one day duration. Temp 104.4° Pulse 120 Resp 40 Pneumothorax, —6—3—5—2, 700 cc. Great deal of pain in right chest for several days, relieved somewhat after pneumothorax. Temperature dropped almost to normal in 12 hours, but then rose to around 101.2° with otitis media present. Septic temperature for six days after collapse, right ear draining profusely. Moderation of chest symptoms suggested that fever was probably due to otitis media. Pneumonia was apparently terminated in 48 hours, right earache on second day, paracentesis on fourth day. Roentgen-ray showed complete recovery.

Case 9 F L, poorly developed, undernourished school boy, 12 years old. There was an indefinite diagnosis of "pneumonia" in early childhood but his recent health had been fair. "Poor hearing" for years without definite diagnosis or treatment. Pneumonia of four days' duration, on left side. Pain in left chest quite severe with pleural friction rub and cough but confirmatory evidence was not as conclusive as in most cases. Temp 103° Pulse 110 Resp 40 Pneumothorax, —4—3—3—2, 300 cc, was followed by some relief of pain. Twenty-four hours later, —3—1—2— $\frac{1}{2}$, 250 cc. Apparent improvement in chest symptoms but in meantime both ears required opening and drainage prolonged. The day after the last injection there was fluid in pleural space with undramatic spontaneous pneumothorax. Fluid rapidly turned to pus containing streptococci. When fluid was sufficiently thick a tube was inserted and this is still draining. Artificial pneumothorax in a moderately severe pneumonia terminating in spontaneous collapse, empyema and drainage. Recovery with minimal disability.

Case 10 L C, fairly well developed and well nourished school boy, 10 years old. Father has pulmonary tuberculosis—present condition not known. The patient had pneumonia at the age of five months and has wheezed a little ever since. At the age of six years he developed what was called bronchial asthma, but a change in climate brought relief in a few months. He had recently been in good health. There was a moderately severe right-sided pneumonia of four days' duration—no asthma. Temp 102.4° Pulse 139 Resp 36 Pneumothorax, —4—3—3—1, 275 cc. After the first treatment the temperature went to 106°. Twenty-four hours later he felt better, and a second treatment was given, —3— $\frac{1}{2}$ —2+2, 200 cc. Complained considerably of adhesion pains. During the following days he became very asthmatic and was not relieved by medication. No further pneumothorax was given on account of asthma. The temperature continued high for five days after first pneumothorax treatment, then dropped and the patient made an uneventful recovery. Chest examination still showed many coarse rales on right with sonorous rales on both sides. This was a case of moderately severe pneumonia in an asthmatic with total duration of fever nine days.

Case 11 M P, rather thin, poorly developed school girl, 11 years old. Right-sided pneumonia of four and one-half days' duration. Extremely ill with delirium for several days. Temp 104.4° Pulse 133 Resp 32 Pneumothorax, —4—3—2—1, 300 cc. Not much change in condition, and a second treatment given 24 hours later, —3 $\frac{1}{2}$ —2— $\frac{1}{2}$ —0, 350 cc. Pain in chest was relieved after this treatment but condition remained very serious. After another 24 hours, third treatment —3—1—1+2, 300 cc, followed by improvement. Two days later —2— $\frac{1}{2}$ —0+ $\frac{1}{2}$, 300 cc. By this time her condition was apparently much better with less cough, no pain and the temperature almost normal. A few days later the pain in right chest returned and a sample of sterile fluid removed. Roentgen-ray examination indicated a spontaneous collapse had taken place at some time as she seemed to have more air in the chest than could be accounted for by treatments and there was change from previous roentgen-rays. However, pressures when sample was taken were —2 $\frac{1}{2}$ —1. Condition little changed for period of a few days when

temperature again rose to 102° – 103° and remained so for a period of three weeks. Chest fluid still remained clear and sterile, but in a specimen 10 days later streptococci were found. This fluid gradually thickened and a tube drainage was instituted 55 days after the original pneumothorax. Condition thereafter was greatly improved. This was a case of very severe pneumonia given four pneumothorax treatments, with evidence of very few adhesions, terminating in spontaneous collapse and empyema.

Case 12 M H, healthy child, five years old. Moderately severe pneumonia of left lung of four days' duration. Temp 103.4° Pulse 130 Resp 48. Pneumothorax, —4—2—2—1, 250 cc. Not much change in condition after pneumothorax. Eighteen hours later, —2— $\frac{1}{2}$ —1+1, 175 cc. Temperature was normal 32 hours after last treatment, and the child made an uneventful recovery. Moderately severe left-sided pneumonia in a child, given two pneumothorax treatments. Total duration of fever six and one-half days.

Case 13 E J, healthy boy, eight years old. Moderately severe right-sided pneumonia with considerable pain of three days' duration. Temp 103.6° Pulse 102 Resp 42. Pneumothorax, —4—2—2—1, 250 cc. Pain relieved. Twenty hours later —3 $\frac{1}{2}$ —2—2—1, 300 cc. Twelve hours later temperature normal. Uneventful recovery. A case of right-sided pneumonia of moderate severity, two pneumothorax treatments, total duration of fever four and one-half days.

Case 14 B M, healthy girl, six years old. Left-sided pneumonia of four days' duration. Extremely ill. Temp 105° Pulse 128 Resp 32. Pneumothorax, —4—3—2 $\frac{1}{2}$ —1, 225 cc. No improvement shown. Twenty hours later pneumothorax, —3 $\frac{1}{2}$ —2—1 $\frac{1}{2}$ —1, 225 cc. Condition unfavorable and low leukocyte count. Twenty-four hours later, —2— $\frac{1}{2}$ —1—0, 225 cc. Temperature dropped quickly to normal after last treatment and the patient made an uneventful recovery. Severe left-sided pneumonia, three pneumothorax treatments, total duration of fever six and one-half days.

Case 15 F W, strong healthy boy, six years old. Moderately severe left-sided pneumonia of five days' duration. Temp 105° Pulse 130 Resp 42. Pneumothorax, —4—3—2 $\frac{1}{2}$ —1, 225 cc. Marked improvement in condition. Twelve hours later, —4 $\frac{1}{2}$ —2—2— $\frac{1}{2}$, 250 cc. Temperature was normal 12 hours after second treatment and the patient made uneventful recovery.

Case 16 E M, healthy boy, three years old. Severe left-sided pneumonia with consolidation of entire lung shown by roentgen-ray. Patient almost moribund. Temp 103.4° Pulse 106 Resp 55. No free space found on first attempt at pneumothorax. On second trial 125 cc given, after which readings were +1+2. Continued attempts at another treatment 24 hours later and 100 cc injected. Final pressure readings +1+2. Patient apparently became somewhat less toxic for about a week then an increasingly high septic temperature developed. Aspiration yielded pus. Roentgen-ray and fluoroscopic examination indicated more air in chest than had been given—possible spontaneous collapse. Condition became more toxic and tube was inserted one month after original pneumothorax. During the next month little change in condition except a severe buccal infection with whitish non-diphtheritic membrane. Died two months and five days after pneumothorax. This is an example of desperately ill pneumonia with almost a completely stuck lung, pneumothorax attempted with small amount of air injected, ending in empyema and death.

Case 17 D N, well developed, plump girl, 11 years old. Right-sided pneumonia of eight days' duration, roentgen-ray showed basal fluid-like opacity. Temp 103.2° Pulse 130 Resp 46. Pneumothorax was attempted in two places and lung was found completely adherent. Next day condition was so very critical that another attempt was made, 200 cc of air being given with final pressure reading of +1+3. Roentgen-ray showed a small pocket at base and 48 hours later as cough and general condition were very bad, another pneumothorax was given, —1+1+6+7, 150 cc. Roentgen-ray showed upper lobe adherent. Temperature gradually receded and

patient was clinically better over period of one week. Then she developed pus in pneumothorax pocket and roentgen-ray indicated a spontaneous collapse. When pus was washed out, a pleural bronchial fistula was demonstrated. Septic rising temperature necessitated insertion of tube 22 days after admission. Case of desperately ill right-sided pneumonia with markedly adherent lung crowded for pneumothorax and ending in spontaneous collapse, empyema, and death.

Case 18 A. A., healthy boy, 12 years old, who had recently recovered from otitis media. Right-sided pneumonia of seven days' duration. He was extremely ill, delirious, with a bad prognosis. Temp 102°. Pulse 120. Resp 40. Pneumothorax, —4—2 + 2+3, 175 c.c. Temperature reached normal 14 hours after treatment and he proceeded to uneventful recovery. Total duration of fever seven and one-half days.

DISCUSSION

The number of cases is small, but presents suggestive evidence. There appears to be a difference in the results obtained in the patients under the adult and childhood groupings. It happened that the adults had had pneumonia for an average period of 3.5 days, while the children averaged 4.7 days. This difference in the duration of the pneumonia before pneumothorax may have been a factor in the difference in the results obtained in the two groups.

The eight adult cases included five with greater or less adhesions, but in none was adequate collapse prevented. Of the 10 children listed, five had adhesions. To this number might be added two cases of pneumonia which were so adherent that no air was given, they were therefore not included in this group. This would make seven cases with adhesions out of 12 children in which pneumothorax was attempted. Of these adherent cases, numbers 16 and 17 were so adherent that only a small amount of air was injected under positive pressure. Both developed empyema and died. In retrospect, we should have desisted here even though the patients were in extremis. There were, therefore, four out of 12 which were so adherent that pneumothorax could not be given. The element of chance must be considered in viewing the difference between 100 per cent adequate collapse in adults and 66 per cent in childhood, but it probably does not account for the marked disparity.

There were no cases of spontaneous collapse nor of empyema in adults, while the latter developed in four out of 10 children. Three of these four definitely followed spontaneous collapse. The fourth might have done so but this is not certain. There were two instances of spontaneous collapse in cases without evident adhesions. Spontaneous collapse seems to be a real danger even in the absence of such an obvious warning signal as mounting pressure from adhesions. Just why it appeared more frequently in children than in adults is not clear, but it is perhaps due to a greater toughness of the pleura in adults. The technical difficulty in giving pneumothorax to an apprehensive child is self-evident and some of the children required two attendants to restrain them. However, the three spontaneous

cases were among the oldest children, two of them being 11 and the other 12 years old. They gave absolute cooperation during pneumothorax and there was no difficulty on account of movement of the patient. It would not have been surprising had spontaneous pneumothorax taken place in some of the smaller, very frightened children who struggled, but this was not the case.

There were two cases among the adults in which two c.c. of tea-colored sterile fluid were withdrawn before the first pneumothorax treatment. In both cases the fluid disappeared spontaneously. The four cases of empyema among the children all started with clear fluid which later turned into pus. In one case the fluid remained sterile for about a month before the first evidence of bacteria was found.

The presence of fluid or pus in six out of 18 cases, 33 1/3 per cent, as compared with cases of pneumonias treated otherwise, is striking. The figures of Rufus Cole of 9.2 per cent in 770 cases, or 6.25 per cent in 24,511 collected cases by Musser and Norris, need only to be quoted to see how excessively high is our incidence. Making all allowances one must suspect that the probability of empyema in pneumonia is increased by pneumothorax. Cases 16 and 17, in which great difficulty was encountered in giving the air, terminated fatally. Both were almost moribund when pneumothorax was attempted. Had we desisted when the difficulty was encountered, they would not have been listed with treated cases, and there would have been no mortality. By including them the mortality for all treated cases was 11 per cent. In the same hospitals at the same time were 15 cases of pneumonia treated without pneumothorax. In this group were six deaths, or a mortality of 40 per cent. The mortality figures given for pneumonia from year to year and decade to decade vary from 25 to 35 per cent. The mortality of our group has certainly been greatly reduced.

The possibility of hastening the crisis by pneumothorax is difficult to estimate accurately. In the first place the actual duration of the pneumonia previous to pneumothorax is often hard to determine. Furthermore, untreated cases of pneumonia vary greatly in their duration and many of our cases must have been near their crisis when first seen by us. In several of our cases the sharp drop in temperature within 24 hours was striking. If cases can be seen earlier it will be easier to determine this point. Our adults were seen after three and one-half days of pneumonia and the total length of pneumonia averaged five and one-half days, which would seem to be less than the average untreated case. Our children were seen after four and seven-tenths days and their average total time was six and two-thirds days which is probably not very different from the duration of cases treated by other means.

Pneumothorax seems definitely to help limit the pneumonic process as none of our cases spread into new non-affected lobes, whereas this is a common occurrence in untreated cases. Furthermore it seems to lessen the toxemia even when the crisis is not immediately brought about. The pa-

CHART III

| No Age Type | Day of Pneumonia | | | | | | | | | | | | Result |
|-------------------|-------------------------------------|-----------------------------|------------------------|------------------------|-----------------------------|------------------------|--------------------|------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | |
| No 3 35 II | | | | 17850 80 49 | | | N | | | | | | Good |
| No 4 20 IV | | | | | P 17000 91 24 | P N | | | | | | | Good |
| No 5 32 III | P 17600 78 34 | P 14000 88 57 | P 16000 78 42 | P 18000 95 46 | P 17600 93 43 N | 15800 89 44 | 18000 90 30 | 17000 84 31 | 17000 76 21 | | | | Good |
| No 6 24 | | 26200 88 | | P | N | | | | | | | | Good |
| No 7 17 | | | 14150 80 | | P 13200 76 | P 10100 83 | 9400 56 N | | | | | | Good |
| No 8 36 IV | P 36020 92 N from lungs | 24500 92 T up ears | 20050 87 | | | | N after ears | | | | | | Good |
| No 9 12 | | | 21000 91 | P | P | EMPYEMA SPONTANEOUS | | | | | | | Empty |
| No 10 10 | | | | P 9600 74 | P 6600 75 | Asthma | | N | | | | | Good |
| No 11 11 | | | | P | P 8700 77 36 | P 16050 85 53 | 11600 75 | P 22200 80 38 | 19600 79 38 | 17500 86 25 | 17300 50 28 | 15000 76 36 | Empty Recovery |

CHART III—Continued

| No Age Type | Day of Pneumonia | | | | | | | | | | | Result |
|--------------------|------------------|---|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|----------------------------|------------------------|------------------------|-------------------------|
| | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| No 12 5 | | | P 25800 90 52 | P 30200 84 36 | P 19850 85 N | P 25000 90 32 | P 17000 79 28 | P 16500 72 40 | P 13200 75 20 | P 9800 69 23 | | Good |
| No 13 8 | | | P 17200 90 42 | P 19800 88 N | P 19200 89 28 | P 12600 86 54 | | | P 13200 76 31 | | | Good |
| No 14 6 | | | P 11950 77 50 | P 9500 76 40 | P 9000 72 32 | P 10600 80 42 | P 15000 84 42 | P 13400 89 38 | P 5600 54 20 | P 7400 36 22 | P 6000 67 58 | Good Good |
| No 15 6 | | | | | P 24150 43 | P 21000 26 N | | | P 12600 69 38 | P 16400 58 30 | P 17000 62 38 | Good |
| No 16 3 | | | | P 25400 87 58 | P 15400 91 49 | P 11800 78 62 | P 11600 82 60 | P 17800 91 10 | P 14000 80 36 | P 16000 66 46 | P 13600 86 35 | Empyema and Death |
| No 17 11 III | | | | | | | P 12800 88 39 | P 21400 87 69 | P 21600 68 60 | P 26400 78 36 | P 46800 87 56 | Empyema and Death |
| No 18 12 | | | | | 18250 90 | | P 31500 93 | N | Spontaneous 12850 69 | Spontaneous | | Good |

P in corner—Pneumothorax

N—Normal temperature

First Number—W B C

Second Number—% Polynuclears

Third Number—% Non-Filament

tient feels better, appears brighter, eats with more relish and can be induced to take his fluids more readily. In practically all cases the breathing is easier, the rate lessened and the depth increased very definitely. This is probably explained by the fact that relief of pain is usually accomplished by separation of the pleural surfaces with air.

From the study of our pictures after absorption of the air and the apparent lack of late complications, there is a suggestion that we may expect fewer abscesses and less bronchiectasis afterward. Complete resolution shown by roentgen-ray took place in 10 to 14 days in a number of cases. The determination of this point will require study of a great many cases over a considerable length of time.

The technical difficulties of artificial pneumothorax increase as the age of the patient diminishes and it would seem advisable that one should not attempt the procedure unless he has had a fair experience in giving artificial pneumothorax especially if the patient is a very small child.

The accompanying chart shows the blood pictures with the high total white blood cell count, the high polynuclear count, and high non-filament count. The higher the non-filament count, the graver apparently is the prognosis. In only two patients did the count reach 60 per cent and both died. However, several very sick patients reached almost this figure during their worst period. Almost invariably the non-filament count recedes as the case becomes better. The white cell count continues high for some time after the crisis and usually the count was still much elevated when the patient was discharged from the hospital apparently well.

In conclusion we would urge that for a proper evaluation of pneumothorax in the treatment of pneumonia, the method be tried early in the course of the disease and the results checked carefully against a control series.

CONCLUSIONS

- 1 Artificial pneumothorax causes a marked reduction of pleurisy pain in lobar pneumonia, and it improves the depth of respiration.

- 2 It lessens the toxemia.

- 3 It seems probable that the duration of pneumonia is shortened, and that at times the crisis is brought about with dramatic suddenness.

- 4 In this series less difficulty was encountered from adhesions in adults than in children and there were fewer complications.

- 5 The danger of spontaneous collapse and empyema is increased in children.

- 6 Total mortality is decreased by use of pneumothorax and the chance of late complications such as abscess, bronchiectasis, or unresolved pneumonia, is probably reduced.

- 7 Spreading involvement to new lobes is checked.

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BEER IN THE DIABETIC DIET ¹

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WITH the return of the legal use of alcoholic beverages in this country, we were faced by questions from many diabetic patients regarding the inclusion of these materials in their diet. The literature contains ample references to the use of alcohol and alcoholic beverages by diabetics, and we shall not attempt to review the bibliography, which is appended below for the convenience of those who are interested. Suffice it to say that, while the pure forms of alcohol have been generally considered to be permissible, and may even be of some therapeutic value in severe diabetes and in diabetic coma, opinions as to the use of beer have differed.

The objections to beer apparently rest chiefly on its relatively high content of grain extractives, which may give rise to sugar in the diabetic organism. It seemed to us, however, that the liberalization of the diabetic diet within recent years should render this a much less serious indictment than in the pre-insulin days. We therefore thought it worth while to study the effects of beer in the contemporary diabetic regimen.

METHODS

Four male patients were maintained in the Max Pam Metabolism Unit throughout the entire experiment. After suitable preliminary and control periods, during which the diabetic status of each patient was stabilized and determined, beer was either added to the diet or substituted in the diet so as to leave the total caloric intake (except for the alcohol) unchanged. When beer was given, one 12 ounce bottle was allowed with each meal, so that the patient received 36 ounces per day.

In the two earlier experiments the so-called "32" beer was used, in the other two experiments beer of higher alcoholic content was given.[†] The following is the relevant portion of the analysis of the "32" beer as furnished us by the Wahl-Henius Institute, Chicago:

| | | |
|---|-------|-------|
| Specific gravity | 1.01 | |
| Alcohol by weight | 3.01% | |
| by volume | 3.86% | |
| Extractives (dissolved solids exclusive of alcohol) | 5.37% | |
| Reducing sugar, as maltose | | 1.64% |
| Pentosans | | 0.42 |
| Dextrins | | 2.30 |
| Proteins | | 0.49 |
| Ash | | 0.19 |
| Acidity (as lactic acid) | | 0.12 |
| Glycerin | | 0.21 |

* Received for publication September 15, 1934.

From The Max Pam Unit for Metabolic Research, Michael Reese Hospital, Chicago.

† In both cases the beer was of the "Rheingold" brand, kindly furnished us out of stock by the United States Brewing Company, Chicago.

The glucose equivalent of this beer, exclusive of the alcohol and ash and including 58 per cent of the protein, was calculated to be about 18 grams per bottle. The analysis of the stronger beer did not differ materially except for its alcoholic content (3.51 per cent by weight, 4.52 per cent by volume) and the same figure of 18 gm carbohydrate equivalent per bottle was used in substituting it in the diet. The alcoholic portion of the beer was not included in these calculations because, as many workers have shown, alcohol is well tolerated and does not form sugar in the diabetic and we were therefore particularly interested in the non-alcoholic fractions of the beer.

RESULTS

The results are given in table 1. The figures for urinary nitrogen and sugar excretion are the averages of daily determinations for the number of days specified in each period. The fasting blood sugar values are averages of analyses made twice a week during each period.

It may be seen that in the first patient (G. L.) the addition of 36 ounces of "3.2" beer to the diet was followed by no change in the sugar excretion but a surprising fall in the fasting blood sugar level. We are unable to explain this fall in the blood sugar, but that it is *not* due to some therapeutic action of the beer seems clear from the next patient (R. T.) in whom the addition of the same amount of beer caused a slight rise in both the fasting blood sugar level and the glycosuria. Furthermore the last control period on patient R. T. shows that he tolerated the addition of an equivalent amount of carbohydrate to his diet, quite as well and perhaps better than when beer was added. The fourth patient (E. A.) showed a definite increase in both the blood sugar level and glycosuria when the "strong" beer was added to the diet.

The substitution of the "strong" beer for an isocaloric amount of carbohydrate in the diet of the third patient (C. W.) produced a hardly significant rise in the fasting blood sugar level and in the glycosuria. In the fourth patient (E. A.), in whom the addition of the "strong" beer had raised the blood sugar level and the glycosuria, both values returned towards the control figures when the same amount of beer was substituted in the diet.

Since in our calculations no account has been taken of the caloric value of the alcohol contained in the beer, it is evident that our patients were able to utilize these additional calories without forming extra sugar and without requiring more insulin. This extra source of calories amounts to the not inconsiderable sum of about 228 calories per day for the "3.2" beer, and 265 calories per day for the "strong" beer. While this source of energy may be of no special value in treating our particular cases, it might conceivably prove to be of practical importance in cases which are just on the borderline as regards their need for insulin to handle an adequate caloric intake.

TABLE I

| Patient | Period of Experiment | Duration of Period | Diet | | | | | | Daily Insulin | Fasting Blood Sugar | 24 Hour Urine Excretion | |
|---------|---|--------------------|----------|-----------|-----------|------|-------------|------------|---------------|---------------------|-------------------------|------------|
| | | | P | r | C | Cals | Beer | Total Cals | | | Nitrogen | Sugar |
| 1 G L | Control Beer ("3 2") | Days 12 21 | Gm 60 | Gm 150 | Gm 100 | 1990 | 0 | 1990 | Units 30 | Mg % 253 | Gm 3 82 | Gm 0 55 |
| | | | 60 | 150 | 100 | 1990 | Added | 2206* | 30 | 87 | 5 86 | 0 66 |
| 2 R T | Control Beer ("3 2") Control Control | 16 | 70 | 100 | 125 | 1680 | 0 | 1680 | 10 | 143 | 11 27 | 4 08 |
| | | 12 | 70 | 100 | 125 | 1680 | Added | 1896* | 10 | 166 | 10 76 | 7 93 |
| | | 15 | 70 | 100 | 125 | 1680 | 0 | 1680 | 10 | 150 | 10 82 | 2 16 |
| | | 10 | 70 | 100 | 179 | 1896 | 0 | 1896 | 10 | 140 | 9 20 | 3 36 |
| 3 C W | Control Beer ("strong") | 9 | 75 | 120 | 120 | 1860 | 0 | 1860 | 90 | 229 | 9 12 | 3 51 |
| | | 7 | 75 | 120 | 66 | 1644 | Substituted | 1860* | 90 | 255 | 8 54 | 6 82 |
| 4 E A | Control Beer ("strong") Beer ("strong") | 19 | 70 | 100 | 125 | 1680 | 0 | 1680 | 60 | 180 | 9 63 | 2 06 |
| | | 9 | 70 | 100 | 125 | 1680 | Added | 1896* | 60 | 241 | 9 50 | 8 27 |
| | | 20 | 70 | 100 | 71 | 1464 | Substituted | 1680* | 60 | 193 | 9 80 | 4 28 |

* These figures do not include the caloric value of the alcohol, which amounts to 228 calories for the "3 2" beer and 265 calories for the "strong" beer per day

SUMMARY AND CONCLUSIONS

Our results show no effects of beer, either harmful or beneficial, in the diabetic diet. To the extent that the alcohol contained in the beer may be utilized without forming sugar and without requiring additional insulin, beer may offer an advantageous source of extra calories in some cases. Our results indicate that, while some patients may probably take moderate amounts of beer in addition to their diet, it is wise to substitute it in isocaloric amounts (exclusive of the alcohol) for other foodstuffs in the diet, as one would do in dealing with any other special article of food.

We are indebted to the Department of Chemistry for aid with the chemical determinations.

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THE DIAGNOSIS OF CARDIAC ANEURYSM WITH REPORT OF TWO CASES¹

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THERE are comparatively few reports of aneurysms of the heart in American literature. The condition is not common, and most of the reported cases are foreign. In a review of 12,000 autopsies Lucke and Rea¹ found 321 instances of all aneurysms. Of this number only 15 were cardiac, indicating an incidence of 1.25 per 1,000 autopsies and 4.64 per cent of the total number of aneurysms.

According to Sternberg² 84.6 per cent of aneurysms of the heart are produced by coronary artery disease. Because of the greater incidence of coronary disease in males, cardiac aneurysms occur more frequently in this sex. In a review of 112 cases Hall³ found 74 per cent in males and 26 per cent in females. Sternberg found 65 per cent in males and 35 per cent in females. Its occurrence is almost entirely confined to the arteriosclerotic age, if we disregard the rare congenital aneurysms and those produced in the course of endocarditis, especially the subacute bacterial form, as reported by Wilson⁴. There are exceptional cases in which the condition was produced by injury. Preble⁵ reported one in a boy, 10 years old, who developed an aneurysm of the left ventricle following a bullet wound, Joachim and Mays,⁶ another in a man 25 years old, in whom at post mortem a calcified aneurysm was found on the anterior wall of the left ventricle, which they assumed was due to an injury of the chest at 12 years of age.

Most of the reported instances have neither been diagnosed nor even suspected during life and were accidental postmortem findings. In a series of 300 such cases, Pletnew⁷ found that only six (0.5 per cent) were diagnosed during life. There are a few other reported cases that were diagnosed or suspected before death. Most diagnoses were made by radiologic means. Thus Steel⁸ reports six cases, all undiagnosed clinically, five of which were detected by roentgen-ray, and three proved by autopsy. One was not shown by roentgen-ray but was found at autopsy. Lenk,⁹ Albrecht,¹⁰ Groedel,¹¹ Branchi,¹² and Fogel¹³ report single cases that were diagnosed radiologically but not clinically.

There are a few cardiac aneurysms reported that were diagnosed clinically. Some of these had very marked signs such as bulging pulsations that could not be missed. In others the diagnosis was based on careful examination and the detection of unusual signs suggestive of the condition. Apparently the first case so diagnosed was that of Remlinger¹⁴. Later Voelcker¹⁵ reported two cases, Queralto¹⁶ one, Sternberg² one, Harvier and

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Caroli¹⁷ one, Smith¹⁸ one, Pletnew⁷ two, and Lutenbacher¹⁹ two cases that were diagnosed clinically and confirmed at autopsy Christian and Friks²⁰ reported a case diagnosed by roentgen-ray but the autopsy findings showed the aneurysm to be in a different location from that indicated They conclude that it is impossible to make a diagnosis of cardiac aneurysm by physical findings

The reason for the failure in diagnosis is that there are no constant clinical signs characteristic of the condition The predominant symptoms are merely those of the late stages of coronary artery disease In many instances, such as in the cases reported by Hughes,²¹ Wilson²² and others, there were no noticeable symptoms present until death caused by rupture of the aneurysm

Because of the rarity of the disease and the greater rarity of a correct clinical diagnosis, we wish to report the following two cases which were diagnosed clinically The roentgen-ray findings in one case were negative and in the other case indicated an aneurysm In both cases the autopsy findings confirmed the diagnosis

CASE REPORTS

Case 1 S M an Italian laborer, aged 33 years, entered the Coney Island Hospital February 7, 1934 and died March 1, 1934 On entrance he presented a right hemiplegia and loss of speech His family history was essentially negative, as was his past history until two months before he came to the hospital At that time the patient was suddenly seized with severe precordial pain, marked dyspnea, cyanosis and vomiting He remained in bed several days Since that time he had been having repeated attacks of precordial pain which occurred with increasing frequency No signs of decompensation developed About a week before he was seen by us the patient had an attack of severe cough, with bloody (?) expectoration, and fever The night before, a doctor had seen him and made a diagnosis of "resolving pneumonia" At 10 00 a m on February 7, 1934 the patient woke up with a hemiplegia and was unable to speak He also developed some dyspnea He entered the hospital at 2 00 p m on that day On examination he was fully conscious and cooperative but unable to speak He was somewhat drowsy but could be readily aroused He was moderately dyspneic and cyanotic His pupils reacted to light and in accommodation The ears and nose were negative The tongue was moist, covered with a brownish fur and protruded in the middle line, the throat slightly reddened There was paralysis of the lower two-thirds of the right side of the face and of the right arm and leg with exaggerated deep reflexes and positive Babinski sign on that side The heart was enlarged to the left, had a gallop rhythm, and the sounds were hardly audible A soft systolic murmur was heard at the apex which was not transmitted to the axilla The lungs showed dullness on the right side posteriorly from the angle of the scapula to the base, with numerous crepitant rales and vesicular breath sounds There were also some rales at the left base posteriorly The abdomen was relaxed and no tenderness was encountered The liver edge was palpated about four cm below the costal margin, the spleen not felt The genitalia were normal and nothing unusual was noted on rectal examination No lymphadenopathy was present There was no peripheral edema The temperature on admission was 101.4° F, pulse 104 and respirations 40 Blood pressure was systolic 110 over diastolic 90 The blood red blood cells numbered 3,000,000, white blood cells 12,600 with 66 per cent polymorphonuclears, hemoglobin 58 per cent (Sahli) Wassermann test was negative The urine and the blood chemistry examinations showed nothing abnormal

On February 8, 1934 the patient was definitely cyanotic, his breathing was rather harsh, and his heart was enlarged to the left with marked prominence and heaving impulse at the apical region. A soft systolic murmur was heard at the apex, accompanying a very weak first sound and there was a presystolic gallop rhythm. We made a diagnosis of recurrent coronary occlusion, apical aneurysm of the heart, mural thrombi in the left ventricle with embolism to the left middle cerebral artery, possible old pulmonary embolism with infarction, congestive heart failure.

In a few days the general condition of the patient improved, and he became less cyanotic. At the end of a week he was able to articulate a few words and recovered some power in the right leg. The heart sounds also improved slightly. Throughout the rest of his stay in the hospital his temperature ranged from 98.6° F to 102° F, pulse 80 to 110, and respirations 18 to 36. The blood pressure varied from systolic 100 to 106, diastolic 88 to 90. Subsequently he had repeated attacks of precordial pain with occasional dyspnea and slight cyanosis. On February 22 he had an attack of nausea and vomiting which persisted intermittently until death. The pain in the precordium became very severe and constricting on the twenty-third, when he became stuporous and exhibited Cheyne-Stokes respiration with prolonged apneic periods. His color was definitely ashen. The heart findings were practically the same, except that the sounds were more muffled. He continued to vomit at intervals and the precordial pain, which later radiated to the abdomen, became progressively worse until his death, March 1, 1934.

A roentgen-ray (portable) examination was made on February 23 (figure 1) and was commented on as follows: "The heart is rather markedly enlarged, particularly to the left, the enlargement being predominantly left ventricular. There is otherwise no unusual deformity of the cardiac shadow. The arch is narrow. The mediastinum and diaphragm appear to be normal. There is a marked degree of pulmonary congestion present with slight pleural thickening, particularly between the upper and middle lobes of the right lung. There is no pulmonary infiltration."



FIG 1 Roentgen-ray, antero-posterior position. Heart diffusely enlarged but no deformity of the cardiac shadow seen.

• Electrocardiographic tracings (figures 2, 3, and 4) were made on February 7, 14 and 23. The general features in all three leads were practically the same. There was a regular sinus rhythm, auriculo-ventricular and intraventricular conduction time were normal, slight slurring of the QRS in all leads, major QRS deflection in the

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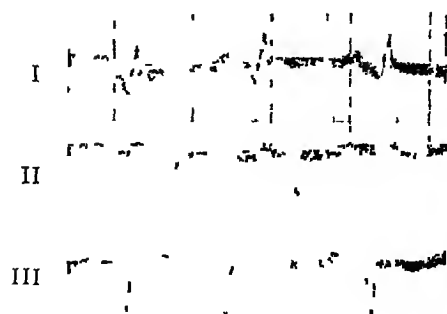


FIG 2

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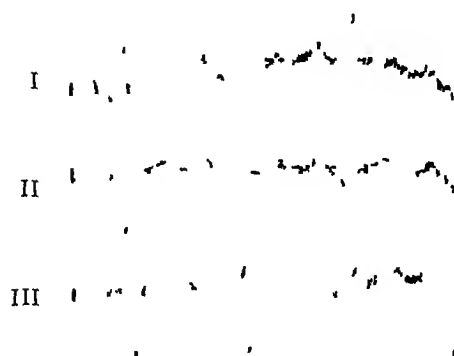


FIG 3

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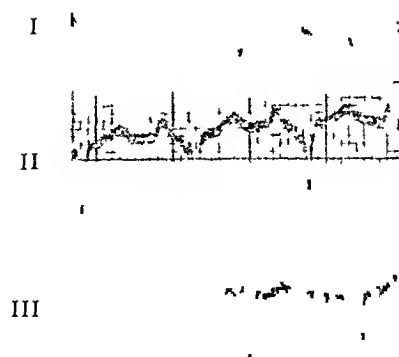


FIG 4

first lead in the form of R-wave and in the second and third leads in the form of S-wave in all tracings. There were, however, some slight variations in the T-wave in the various tracings. On February 7 the T-wave in the first lead was isoelectric, in the second lead it was nearly isoelectric, and in the third lead it was of low voltage. On February 14 there was a tendency for the T-wave in the first lead to be slightly positive, in the second and third leads it was definitely positive, but of low voltage. On February 23 the positivity of the T-wave was more pronounced. The voltage of the QRS complexes in all leads was somewhat higher on February 14 and 23 than on February 7. There were also some minor variations seen in the P-waves in the two subsequent tracings as compared with the first tracing. In general, the electrocardiograms showed evidence of marked myocardial disease of a rather chronic nature, inasmuch as it did not show progressive changes that are often seen in acute coronary occlusion.

Necropsy was performed by Dr Harold Fink. Section of the head was not permitted. The left pleural cavity contained about 200 cc of straw-colored fluid. The lungs showed marked congestion. The heart (figure 5) weighed 450 gm. The pericardium was adherent to the lower half of the anterior surface of the left ventricle. There were numerous petechial hemorrhages over the posterior surface of the epicardium. The tricuspid valve was of usual appearance, and the right auricle of average size. The wall of the right ventricle measured 0.4 cm in thickness. The septum bulged into the right side of the heart. The pulmonary vessels were of average size, and the branches of the artery showed no obstruction nor thrombus formation. The pulmonary valve leaflets were normal. The wall of the left auricle was smooth. The mitral valve was translucent. The chordae tendineae were not unusual. The wall of the left ventricle varied in thickness from 1.0 cm to 0.3 cm (at the apex). The lower two-thirds presented a marked sacculation, the size of a medium-sized orange, and filled with postmortem clot. There were several pieces of organized thrombi in the interstices of the trabeculi. The aortic cusps showed moderate atheromatosis and slight loss of elasticity. The commissures and valve



FIG 5 Gross specimen of the heart showing the aneurysm (arrows)

edges were of average appearance. The aorta was diffusely atheromatous. The left coronary artery was completely occluded in its entire course beginning about 0.2 cm from its origin. The circumflex branch was partly patent but the anterior descending

branch showed complete organization. The right coronary artery showed a marked diffuse atheromatosis with moderate narrowing of the lumen. The superior and inferior venae cavae were patent throughout.

The liver weighed 1500 gm and had a marked nutmeg appearance with large irregular confluent light yellow areas. The spleen weighed 180 gm. It was firm, the follicles were prominent and there was moderate fibrosis, but no infarct. The combined weight of the kidneys was 380 gm. The capsules stripped with moderate ease, leaving gross scarring of the surface. There was a moderate shading of the cortex into the medulla. There was an increase of pelvic fat. The renal arteries were slightly atheromatous. No other organs showed anything unusual.

Microscopic sections of the heart showed brown atrophy, loss of striations of muscle fibers and marked diffuse fibrosis. In some areas individual nuclei showed karyokinesis and karyolysis. In the liver there was congestion of the central portion of the lobules with atrophy of liver cells. Kidney sections showed hyalinized glomeruli and areas of cloudy swelling and hyaline casts in the tubules.

Case 2 S W, a Russian storekeeper, aged 58 years, was admitted to the Coney Island Hospital on February 22, 1934 and died on April 18, 1934. The essential features in the family history were that a brother died at 56 years of age of gangrene of both feet, one son died at 29 years of pneumonia, one was operated on at 26 years for nephrolithiasis, and a third son died at the Kings Park Hospital for the Insane. His wife at the time of his illness was confined to Kings Park Hospital. He had measles and scarlet fever in childhood and acute bronchitis at 17 years of age. He had suffered an attack of severe precordial pain 15 years before and some palpitation and dyspnea on exertion a week before the present illness. He had smoked about 15 cigarettes per day from early youth.

Present illness On February 21, 1934 at about 10 30 p m while drying dishes at home, he was suddenly seized with a severe vise-like constricting precordial pain radiating upward to the shoulders and down both arms, more to the left than to the right. The attack lasted about 10 minutes and subsided. He went to bed but was awakened one hour later by a recurrence of the same pain. This time it was so severe that he thought he was going to die. This attack also gradually passed off only to return with still greater severity at 4 30 a m on February 22. A physician was called, who administered half a grain of morphine and advised hospitalization. The pain was still continuous at 5 a m when he came to the hospital, and persisted for several hours afterward.

On physical examination the patient appeared acutely ill. His color was ashen and expression anxious, he was not particularly dyspneic. The pupils were equal and regular and reacted to light and in accommodation. The mouth showed pyorrhea alveolaris and many carious teeth. The throat was slightly injected and the tongue dry. The neck showed no adenopathy and no visible pulsation. There was considerable peripheral arteriosclerosis. The heart was moderately enlarged to the left. The first sound was diminished in intensity at the apex and was more intense at the fourth left costosternal junction. The pulmonic second sound was greater than the aortic second sound. The ventricular rate was about 90 and the rhythm was regular. No murmurs were heard. The lungs showed normal resonance and breath sounds. The abdomen was not remarkable. No peripheral edema was present and the reflexes were normal. The temperature on admission was 101.6° F, pulse 86, respirations 20. The blood pressure was systolic 124, diastolic 80. The blood red blood cells 2,000,000, white blood cells 23,000 with 68 per cent polymorphonuclears, hemoglobin 42 per cent (Sahli), Wassermann test was negative. The urine contained one plus albumin but was otherwise normal. The blood chemistry examinations were normal. The diagnosis was acute coronary occlusion.

On February 23 a few inspiratory crepitant râles were heard at the left base. The other findings were the same as on the previous day. A teleroentgenogram on

that day was reported "The heart is moderately enlarged, particularly to the left of the midline. There is slight prominence of the left upper cardiac border. There is some elongation of the aorta. The mediastinum, diaphragm and ribs appear normal. The shape of the heart is not characteristic of any valvular lesion. The lung fields are aerated. There is a slight degree of pulmonary congestion with evidence of chronic bronchitis and slight pleural thickening. There is no significant parenchymal lung infiltration. There are a few areas of discrete fibrosis of the upper lobe. Diagnosis: Cardiac enlargement, elongation of the aorta, pulmonary congestion."

An electrocardiogram (figure 6) on the same day showed slight elevation and coving of the S-T segment in the first lead with negative T-wave formation, elevation and coving of the S-T segment in the second lead with beginning negative T-wave formation, also elevation and coving of the S-T segment in the third lead with beginning negative T-wave formation, there is very faint slurring of the QRS complexes in all leads and negative P-wave in the third lead.

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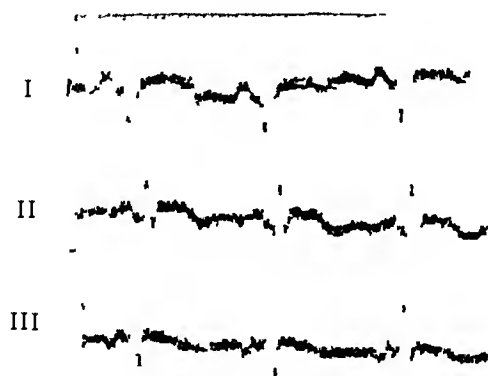


FIG 6

The precordial pain gradually subsided and his condition seemed to be slightly improved during his first three weeks in the hospital. His temperature ranged from 98° to 101.8° F, pulse 70 to 100, and respirations 18 to 24. Blood pressure ranged from systolic 100 to 122, diastolic 64 to 82. On March 12 there was some shortening of the first sound, assuming more or less of a valvular quality. Size and configuration of the heart were about the same.

Other electrocardiograms were made on March 12 and March 21, 1934. Because they were similar to each other, only the latter (figure 7) is herewith reproduced. This tracing shows diminished voltage of the QRS complex in the first lead as compared to the one of February 23 with markedly negative T-wave formation in the first and second leads and isoelectric T-wave in the third lead with return of the S-T segment in all leads to the isoelectric level. The S-wave in the third lead seen in the first tracing has disappeared and there is a definite Q-wave in the tracing of March 21. There is also some slurring of the base of the descending limb of the R-wave in the third lead which is not present in the previous tracing. The P-wave in the third lead which was previously negative has now become diphasic.

On March 17 the patient developed a sore throat and his temperature rose to 102° F. His general condition became slightly poorer. The fever thereafter persisted on a somewhat higher level ranging from 100.6° F to 103.4° F throughout the fifth and sixth weeks of his stay in the hospital. The cardiac findings remained practically the same although there seems to have been some improvement in the quality of the first

sound On April 2 percussion of the heart dullness indicated some bulging of the left border of the heart above the apex There was a presystolic gallop rhythm with marked diminution in intensity of the first sound at the extreme edge of cardiac dullness

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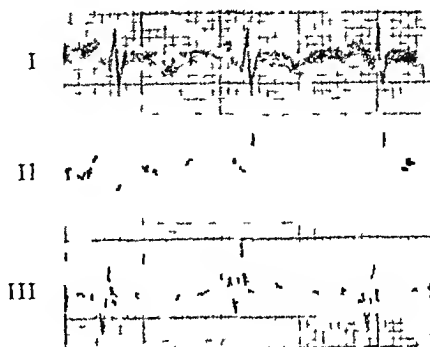


FIG 7

ness Both bases of the lungs showed diminished breath sounds with numerous inspiratory bubbling rales Our diagnosis at that time was left ventricular aneurysm near the apical region with possible mural thrombi, progressive myocardial damage and congestive heart failure

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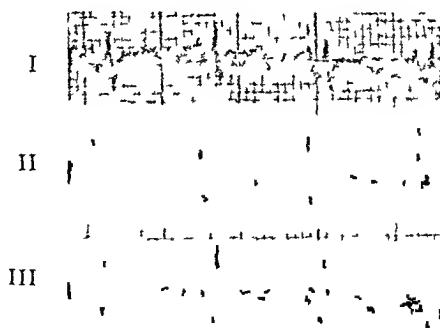


FIG 8

Further electrocardiograms were made on April 2 and again on April 16 Because of their similarity, only the latter (figure 8) is herewith reproduced This tracing shows marked slurring of the QRS complexes in the first lead, positive T-wave in the first lead, isoelectric T-wave in the second lead and negative T-wave in the third lead, all of which differ from the tracings taken on March 21 and indicate progressive myocardial changes At our suggestion another teleroentgenogram (figure 9) was ordered on April 3, with the following report "The film shows practically the same cardiac findings as previously described At this time the bulge in the left cardiac border, which was previously noted, is still seen This prominence is slight and lies in the upper portion of the left ventricular border The appearance is very suggestive of a ventricular aneurysm, particularly since it is present on the previous film as well as on this one"

In view of these findings, Dr Emanuel Mendelson, the radiologist, made a fluoroscopic examination in the supine position. His findings were "The heart is enlarged to the left, amplitude of contractions diminished, the prominence of the upper portion of the left ventricle is seen as noted on film examination and the wall



FIG 9 Roentgen-ray in the antero-posterior position. Aneurysmal bulging area is shown by arrows.

in this region appears definitely weakened and does not contract synchronously with the remainder of the ventricle." His diagnosis at that time confirmed the clinical impression of ventricular aneurysm.

The patient gradually became drowsy and developed marked mental depression, his appetite became poor, his temperature remained about the same. His precordial pain recurred at times and was relieved only by large doses of morphine. By April 16 it had become almost continuous and more severe. His color was ashen, his heart rate was 105, sounds became markedly weakened and the gallop rhythm more pronounced. There was blood tinged expectoration and the lungs showed dullness at both bases posteriorly from the seventh rib to the base on the right side and the eighth rib to the base on the left side, with marked diminution of the breath sounds and râles over these areas and suggestion of a pleural friction rub. Our diagnosis at this time, in addition to the previous diagnosis, was bilateral bronchopneumonia, possible pulmonary embolism, with infarction and bilateral hydrothorax. His condition became rapidly worse and he died on April 13 at 12 30 a.m.

A necropsy, limited to the heart, was performed by Dr Harold Fink. The heart (figure 10) was found to be somewhat enlarged, weighing 400 gm. There was a distinct aneurysmal bulge of the left border beginning about three cm. above the apex, measuring five cm. in diameter and extending one and a half cm. beyond the margin. The ventricular wall in this aneurysmal portion was markedly thinned out, measuring 0.3 to 0.5 cm. in thickness, while the remainder of the wall was two cm. thick. The inner surface of the aneurysm was devoid of endocardium, being covered by a firmly adherent shaggy membrane. The anterior descending branch of the left coronary artery was completely occluded by an organized thrombus which extended from a point 2.5 cm. below its origin through the remainder of its course. The proximal portion of the vessel showed numerous atheromatous plaques, but no fresh thrombi. The right coronary artery showed similar plaques but was patent throughout its course as was also the circumflex branch of the left coronary artery. However, all

the smaller subdivisions of the left circumflex artery running toward the aneurysm were completely occluded. The right ventricle and the valves showed nothing of significance.



FIG 10 Gross specimen of the heart showing aneurysmal area (arrows) in its relation to the apex (A). The greater part of the aneurysm has been removed.

Microscopic section showed sclerosis of all smaller arterioles, diffuse brown atrophy of the heart cells and marked diffuse fibrosis. At the site of the aneurysm the endocardium was absent and there was organized blood clot.

The first case is of particular interest because of the patient's age. Although he was only 33 years old at the time of death, and had comparatively little peripheral arteriosclerosis, the coronary system was markedly sclerosed and occluded. Most of the smaller coronary subdivisions appeared like thin threads, as did the main anterior descending branch of the left coronary artery. Such a degree of coronary sclerosis must certainly have taken several years to develop.

In both our cases, acute coronary occlusion of the anterior descending branch of the left coronary artery was the precipitating cause of the aneurysms. Since, in the first patient, the acute occlusion would seem to have occurred only two months before admission, the aneurysm evidently developed within that period. As for the second patient, however, it is difficult to decide to which attack to attribute the aneurysm—the first, 15 years ago, or the second, just preceding admission. If the former, it is difficult to believe a man could live 15 years with a cardiac aneurysm, and if the latter, it is equally incredible that the aneurysm developed within 36 hours, since the bulge was definitely seen on the first roentgen-ray, taken the day after admission.

The pathogenesis of most reported cardiac aneurysms is myocardial infarction secondary to occlusion of a main coronary branch, in an area already the seat of considerable impoverishment of the blood supply. The subjective symptoms are not specific. Evidences of heart failure in various grades and forms, or the anginal syndrome, although present in most reported cases, are merely expressions of coronary and myocardial disease and occur more commonly without aneurysms. Some of the objective findings, however, are important. In the first of our cases the prominence and the diffuse heaving character of the apical impulse, associated with extreme weakness of the first sound over that area, the presystolic gallop rhythm, the localized systolic murmur, together with the weak pulse were sufficient for us to diagnose the condition even in the absence of positive roentgen-ray findings, and were especially significant with the story of recent acute occlusion and the repeated attacks of precordial pain which followed, all of which indicated to us progressive myocardial changes consequent to repeated occlusive processes of the smaller coronary branches. Likewise, in the second case, the prominence of the left border above the apex, the marked diminution of the first sound at the apex (while at the fourth left costosternal junction it was rather intense), the presystolic gallop rhythm, as well as the history, led us to make the diagnosis. The roentgen-ray findings of a bulging area and the fluoroscopic findings of contraction of this area asynchronous with the remainder of the ventricle were sufficient confirmatory evidence.

The recorded cases in the literature that were diagnosed before death showed noteworthy features. In the case reported by Remlinger¹⁴ there was a feeble heart impulse, weak sounds and occasional pericardial friction rub. Lutenbacher¹⁹ stresses the importance of fixation of the apex impulse due to pericardio-diaphragmatic adhesions and tenderness over this area. Harvier and Caroli¹⁷ found in their case two areas of heaving cardiac impulse, one in the sixth space and the other in the fourth with systolic retraction in the fifth space. In McElroy's²³ case there was an expansile pulsating tumor in the apical region extending to the seventh space as far as the anterior axillary line. This was associated with distant heart sounds, a soft feeble murmur, fixation at the apex and a weak pulse. Libman and Sacks²⁴ and Libman²⁵ mention a pulsation most marked medial to the apex associated with a dull first sound and gallop rhythm as pathognomonic of aneurysm. To quote Libman "if you get a very poor first sound and if you then get a pulsation more marked between the apex and sternum than at apex, there is practically no condition except aneurysm possible." Christian and Frik²⁰ diagnosed their case of aneurysm of the upper portion of the left ventricle by an impulse at the left border. Smith¹⁸ diagnosed his by cardiac weakness and persistence of two points of cardiac impulse together with a peculiar outline by roentgen-ray.

If we bear the condition in mind and if we carefully elicit the physical findings, a clinical diagnosis should be made in many cases of cardiac aneu-

rysm especially at the apical region. The roentgen-ray findings are helpful if corroborative, if not and the physical findings point toward the condition, we may consider it at least as a possible diagnosis. The roentgenograms should be made in the antero-posterior and oblique positions and checked up by fluoroscopic examination. Aneurysms above the apex will in many cases then be diagnosed when the physical findings may be doubtful. Aneurysm of the apex, on the other hand, especially of the lower portion, will often escape detection by roentgen-ray as in our first case, but will have definite physical findings pointing toward it. The usual appearance of ventricular aneurysm is a bulging shadow which follows the heart displacements with changes in respiration and position. On fluoroscopic examination there is found a slackening of the movement of the heart at the area of the aneurysm as in the case of Branchi¹² or there is an asynchronous pulsation with expansion, during systole, as in our second case and in the cases of Groedel¹¹ and Wiberg.²⁶ The density of the shadow varies with the contents of the aneurysm. If filled with organized clot its shadow is more dense and in the lateral view it stands out as an area of increased density superimposed on the cardiac shadow, as in Branchi's case.¹² Very rarely an organized ventricular aneurysm becomes calcified and will show up as such by roentgen-ray, as was seen by Jaksch-Wartenhorst.²⁷

The electrocardiogram offers no specific help in the diagnosis of cardiac aneurysms. In our two cases, as well as in other reported cases, the tracings merely indicate severe myocardial damage. In apical aneurysms, as in our first case, there is a tendency of the major QRS deflections to be directed downward in the second and third leads. This, we believe, is a noteworthy diagnostic sign if taken in conjunction with other evidence. If the pathologic processes in the heart are acute and rapidly developing, we may expect to find the characteristic rapid alterations in the electrocardiographic configurations as in cases without aneurysmal formation.

SUMMARY AND CONCLUSIONS

Two cases of left ventricular aneurysm, diagnosed during life and proved by autopsy, are reported. One is of particular interest because it occurred in a man of 33 years whose heart was the seat of diffuse coronary sclerosis and occlusive processes with myocardial fibrosis. The findings in these two cases together with some observations reported in the literature lead us to the following conclusions:

- 1 Most cardiac aneurysms are left ventricular, predominantly in the apical region, and usually follow acute coronary occlusion.

- 2 The subjective symptoms of cardiac aneurysm are not specific, being merely those of cardiac failure or of the anginal syndrome which may accompany similar cases without aneurysm.

- 3 The clinical criteria for the diagnosis of ventricular aneurysm are a history of coronary occlusion, an abnormal area of cardiac dullness over

which is heard a very weak first sound, associated with a gallop rhythm usually situated near the left sternal border

4 The roentgenographic criteria include a bulging shadow following the heart displacements with changes in respiration and position, and slackening of the movements of the heart or asynchronous pulsation, with systolic expansion in that area. If filled with organized clot, an increased area of density will be seen, and calcification, if present, is suggestive.

5 The electrocardiogram is of no specific diagnostic value. Apical aneurysms, however, seem to be associated with major QRS deflections which are directed downward in the second and third leads and in the first lead with a low voltage, upward. This may perhaps be significant as corroborative evidence.

6 Although only about 0.5 per cent of ventricular aneurysms have hitherto been diagnosed during life, we believe that if the condition is borne in mind and attention paid to the above criteria, the diagnosis will be made with increasing frequency.

ADDENDUM

Since submitting this paper for publication, we observed another case of ventricular aneurysm in a 62 year old man, who entered the Coney Island Hospital on July 10, 1934. Four years before admission he had an attack of coronary occlusion and has since been bedridden most of the time. He has had repeated precordial pain which has become worse during the past year. His heart was enlarged especially to the left and presented a distinct apical bulge and a heaving apical impulse on palpation. The sounds were barely audible and no murmurs were ever heard. Blood pressure was systolic 110, diastolic 70 and there was evidence of congestive heart failure. The diagnosis of apical aneurysm was made on the basis of the history, apical bulging and heaving apical impulse associated with a very weak first sound over this bulging area. The diagnosis was confirmed by roentgen-ray which showed "increased prominence of the left upper ventricular border."

He died on September 19, 1934, and at necropsy there was found an enlarged heart weighing 400 gm., with an apical aneurysm four and a half cm. in diameter. There was overlying pericardial exudate, and a complete old occlusion of the anterior descending branch of the left coronary artery.

It is significant that the location of the aneurysm as revealed by post-mortem examination did not correspond to the location shown by the roentgen-ray but to the location suspected clinically.

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VASCULAR CRISES¹

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ALMOST before we were aware of it, a striking innovation appeared in medical nosography and medical practice. A new specialty has developed which was hardly dreamed of three or four years ago—a specialty dealing with diseases of the blood vessels.

In our textbooks the subject of these diseases, particularly insofar as it concerns the arteries, is dealt with largely as static—uninterestingly and briefly. But within an unbelievably short space of time, disease of the blood vessels has become a dynamic, active branch of medicine with a rapidly growing literature of its own. Some may decry such intensive specialization in medicine, but it cannot be denied that concentration upon one field broadens our knowledge, though it may narrow the broadeners. The new specialty, which might be called angiology, has already a large number of devotees in this country and abroad, and is bringing under its aegis diseases that previously did not seem to have any connection with it. In a number of hospitals special vascular clinics have been created and the men in these clinics are taking their place beside the cardiologists and the allergists.

When we look into the history of the subject we find, as in nearly every other phase or department of medicine or science, that its roots go far back and that we are by no means the pioneers that we may fondly think ourselves. As is pointed out so wonderfully in Thomas Mann's "Joseph and His Brothers," when we come to what seems the beginning of anything in history, it is not the beginning though want of knowledge may make it seem so. Therefore when I start in 1773 with Stephen Hales' "Haemodynamics," it is in implied recognition of Mann's thesis. Hales was seemingly the first to advance the notion that the arteries were contractile. With plain water he perfused an aorta and its mesenteric vessels at a constant pressure head and noted the outflow to be greater when the fluid was warm. Investigating also the effect of alcohol and extract of cinchona bark, he was led to conclude that some drugs caused constriction and some dilatation.

E. H. Weber appears to have been the first to assume a nervous control of contraction, advancing the hypothesis to explain blanching and pallor on one side and blushing on the other.[†] Perhaps before Weber I ought to mention Allan Burns, who in 1809 explained angina pectoris on the basis of a spasmodic contraction of the coronary arteries—a very ingenious and fertile thought. The muscular coat of the arteries was not described until 1840, when Jacob Henle reported its existence, and then Claude Bernard in

* Read at the Meeting of the Interstate Graduate Assembly at Philadelphia, November 6, 1934.

† Thomas Willis (1621–1675) had a working hypothesis of the vasomotor nerves. "These small lines and cords of nerves do variously straighten, compress, or it may be sometimes quite shut these blood-carrying vessels" by acting on the muscular coat of the vessels to which they are distributed.¹

1851 noted the effect of cutting the sympathetic nerve on the vessels of the rabbit's ear and the effect of stimulation of the nerve. With these cumulative observations, the relation of the sympathetic nervous system to the caliber of the blood vessels became firmly established.

The earliest clinical observation—I use the superlative with the reservation mentioned above—is probably that of Charcot in 1858 on Intermittent Claudication,² a condition described as occurring in horses by Boulay in 1831. Four years after Charcot's publication, there appeared what is still the most important essay in the entire field of vascular diseases, namely Raynaud's classical thesis "On Local Asphyxia and Symmetrical Gangrene of the Extremities."³ Goltz in 1874 suggested the existence of a vasomotor mechanism in the peripheral vessels, in the ganglion cells of vasomotor nerves.

The next milestone is represented by Pal's epochmaking monograph on Vascular Crises.⁴ After the lapse of a dozen years, Buerger's⁵ masterly article on Thromboangitis Obliterans appeared and marks another milestone. Since then the literature has grown so fast that it is impossible to do it justice. I shall mention only a few outstanding contributions: Krogh's pioneer work on the capillaries, that of Leriche, the father of sympathectomy, that of Cannon on the sympathetic nervous system and the endocrine glands, that of Sir Thomas Lewis and his associates on the capillaries, that of Brown, Adson and other members of the Mayo Clinic, on various phases of vascular disease, the work of Lichtwitz, Alice Bernheim, Starr, Landis, Scott, Kramer, Herrmann, Bastai and Dogliotti, and many others.

The vasomotor nervous system which has its centers in the medulla and in the spinal cord, is distributed chiefly to the arterioles and capillaries but also to the veins and large arteries. The nervous apparatus in the vessel walls regulates the tonus of the vessels. This tonus, which together with the force of the heart maintains the blood pressure, is very sensitive and is readily influenced by many factors such as hormones, temperature, emotions and sensations, activity of the muscles or of the internal organs, poisons, etc. While the tonus influences the blood pressure, the corollary is also true that the state of the blood pressure reacts upon the sympathetic nervous system and thereby affects the tonus of the vessels. Although the vascular tonus is directly under the influence of the sympathetic nervous system, the latter in turn is brought into action or inhibited, as the case may be, by hormones of various ductless glands—the adrenals, pituitary, parathyroids, sex glands, and thyroid. The study of the interrelation of these glands, a factor in what Cannon calls homeostasis, constitutes one of the most difficult and important biological problems.

The vasomotor nerve impulses seem to reach the vessels along their whole length and not only in a single trunk at the beginning. This is important in connection with sympathectomy—cutting the perivascular nerves of any one segment does not wholly deprive the vessels of their vasoconstrictor innervation. The predominant vasomotor impulses are constrictor in nature,

dilatation of the blood vessels has by some been looked upon as a passive process resulting from inhibition of the vasoconstrictor mechanism, but there is considerable experimental proof that dilatation itself may at times be active. In animals dilatation can be produced by stimulating the central end of the depressor nerve after all vasoconstrictor fibers have been severed. Such a result would imply the existence of a vasoconstrictor center but this conclusion cannot be applied to man without some corroborative observations that are still lacking.

At its bifurcation the carotid artery is somewhat enlarged—the carotid bulb or sinus—and is here surrounded by a plexus of nerves. Pressure upon the sinus causes slowing of the heart and lowering of blood pressure (Czerniak's phenomenon). At first it was believed that the effect was due to direct pressure on the vagus nerve, but Hering, Hymans and others have shown that the effect is due to a reflex stimulation of vagus inhibitory fibers through pressure on the carotid sinus nerves. Very little is known of the share of the carotid sinus in the vascular tonus in man, whether it is constrictor or dilator, or actually, whether it plays any role whatever.

The vasomotor system, including in this the intrinsic and extrinsic mechanisms, is very sensitive. This sensitiveness is well shown in a simple experiment devised by Landis and Gibbon⁶. When the hands and forearms are immersed in warm water, a decided rise in surface temperature occurs in the cool lower extremities within 15 minutes—from 26° C (78.8° F) to 32° C (89.6° F). The reflex effects of cold, acting through the medium of the vasomotor system, are demonstrated in the experiments of Hines and Brown^{7,8}. By putting one hand in ice water for 20 to 30 seconds, an immediate rise in both systolic and diastolic pressure is produced. The response is not augmented by placing both hands or both feet or all four extremities in ice water. It is interesting and for future studies very significant that persons with established essential hypertension and even those in what might be called the functional or preclinical stage of hypertension give an exaggerated response, showing an increased vasomotor irritability.

In a virtually new and not yet overclassified subject such as diseases of the blood vessels a variety of classifications is possible. From a clinical point of view we shall find it advantageous to speak first of all of general and of local vascular crises, which may again be subdivided into constrictor and dilatational crises.

1 *General Constrictor Crises*. These are exemplified by the sudden rises of blood pressure that occur both in apparently healthy and in hypertensive individuals. Among the former it is the lively, excitable, intense type that is subject to sudden rises of blood pressure. These crises are of brief duration and usually pass off without any deleterious effects. It is possible, however, when these crises are oft repeated, especially under the influence of psychic stimulation, as pointed out by Schreiber, that they eventually lead to a permanently heightened tonus, to hypertrophy of the muscular coat of the arterioles, and to hypertension.

In the hypertensive group—and it should be remembered that the blood pressure need not be extremely high—sudden vascular crises may produce a variety of nervous symptoms—headache, vertigo, tinnitus, aphasia, monoplegia, hemiplegia, hemianopsia, convulsions. It may not always be easy to decide whether these symptoms are due directly to a general hypertensive crisis or to localized functional or anatomic changes that precede and cause the rise in blood pressure.

The relation of general hypertensive crises to angina pectoris has recently been studied by Sir Thomas Lewis.

General vascular crises are common in women at the time of the menopause—which makes it highly probable that some endocrine imbalance resulting from atrophy of the ovaries or changes in related glands plays an etiologic role.

General dilator crises manifest themselves in a sudden fall of blood pressure. In practice it may be difficult to decide how much of the fall is due to vascular dilation—whether from constrictor paralysis or dilator stimulation—and how much to cardiac weakness. In the collapse of acute infectious diseases and in traumatic shock vasomotor paralysis is the predominant mechanism, although in the former some element of heart weakness is added. A preliminary vasomotor spasm of the surface usually attends shock. In sudden coronary obstruction, in acute cardiac dilatation, in rupture of the heart, there is a tremendous fall of blood pressure from direct depression of the cardiac function. The symptoms of dilator crises resemble those of severe hemorrhage—profound weakness, pallor, sweating, sighing respiration, dizziness, thready pulse, at times unconsciousness. Dilator crises are produced as already indicated, by acute infections, by shock, traumatic and surgical—toxic agents such as histamine may here play a part—at times by changes in posture (postural hypotension), and by Addison's disease.

2 Local Vascular Crises These are chiefly of the constrictor type, but blushing and other forms of erythema, even the redness of inflammation are examples of local dilatation. While local vascular crises or angiospasm are usually brought about by stimulation of the nervous vasoconstrictor mechanism, a myogenic contraction excited by hormones or other agents is conceivable. Just as we have in the heart a myogenic contraction but one profoundly influenced by nerve impulses, so we may assume a similar mechanism in the arterioles, the muscular coat of which is large in proportion to lumen. Certain individuals, according to Lichtwitz,⁹ suffer from an angiospastic diathesis. They are in consequence subject to angiospasm in various parts of the body, particularly in the veins of the liver and spleen. Spastic closure of these prevents an adequate amount of blood from getting out of the natural reservoirs which in turn leads to anemia or ischemia elsewhere.

The results of spastic contraction as well as of any other form of vascular occlusion depend upon a variety of factors—the size of the occluded

vessel, the duration of the spasm, the previous state of nutrition of the part, and the possibilities of prompt and adequate collateral circulation I once saw the pulse suddenly disappear completely at the wrist through spasm of the radial artery without any observable after-effects In some organs there is so little anastomosis between the vessels of contiguous territories (end arteries) that even a brief obstruction produces functional and usually also structural changes Diseased vessels, unless they have entirely lost their contractile power, are more sensitive to vasomotor influences than normal vessels but, while more responsive, they return more slowly to their previous state Under some conditions vessels, the coats of which are anatomically entirely normal, show a vasomotor hypersensitiveness Such conditions occur in certain constitutions, often on a racial basis, and in individuals of peculiar psychic and physical makeup

It has usually been held that the functional effects of cutting off the blood supply to a territory depend upon the lack of nutritive material, but it is highly probable that it is principally the local deprivation of oxygen that is responsible for the primary results of vascular obstruction *

The subject of local vascular crises is rendered somewhat difficult by the fact that in some territories identical functional results are produced by angiospasm, by embolism, and by thrombosis This is particularly true of the brain What I have to say about the symptoms of cerebral angiospasm may therefore be applied in large measure also to those other forms of obstruction

Cerebral Angiospasm On account of the complexity of the cerebral functions, angiospasm produces a multiplicity of symptoms which have one feature in common—they are as a rule of short duration They occur most frequently in hypertensive individuals, but also in persons whose pressure is not markedly abnormal According to location, we may have monoplegia, hemiplegia, aphasia, hemianopsia and other visual defects, convulsions, and possibly also psychomotor and psychic disturbances There is a good deal of evidence that migraine is dependent upon angiospasm, perhaps allergic in ultimate origin

I have just said that convulsions may be due to angiospastic states The type of seizure I have in mind occurs most often in persons of middle or late life who have suffered long from hypertension, not exclusively, however, for I have seen them in individuals with blood pressures but little above the normal

Those unfamiliar with the convulsions in question are apt to diagnose them as genuinely epileptic or as uremic, the latter especially because a little albumin is usually found in the first urine passed after the fit If one studies the history of these patients, one finds that the convulsions had no connection with childhood and adolescence, that the first seizure occurred in the sixth or seventh decade, and that they repeated themselves at irregular

*For the local deprivation of oxygen to the tissue I have proposed the word *histanoxia* (from *histos*, tissue, *ἀνοξία*, without oxygen) The term *anoxemia* sometimes used for oxygen starvation connotes rather a general state of the blood than a local condition

intervals As a rule, the convulsions leave no aftermath, occasionally some disturbance of speech, of vision, or of mentality persists for a while If the patient is seen just before or during an attack his blood pressure, both systolic and diastolic, will be found raised considerably above its habitual level To distinguish this epileptiform convulsion from true epilepsy, it has been called *epilepsia tarda* or *senile epilepsy*¹⁰

The best treatment for the attack is bleeding from the arm, preventive treatment involves the general measures applicable to hypertension as well as those made use of in true epilepsy.

Uremia and eclampsia are very similar to *epilepsia tarda* and may also represent vascular crises In the diagnosis the convulsions of general paralysis of the insane must also be borne in mind When they are the inaugural symptom, they may, as I have seen, give rise to much perplexity until a positive Wassermann test is obtained with the spinal fluid

A variety of transient sensory and psychic disturbances may have an angiospastic origin—vertigo, tinnitus aurium, hemianopsia, quadrant anopsia, disorders of color vision, amaurosis, and headache Migraine or hemi-crania, as already mentioned, is perhaps an angiospasm on an allergic basis Spasm of the homolateral temporal artery has been observed during the migrainous attack Among psychomotor and psychic phenomena producible by angiospastic states, sensory aphasia, amnesia and brief psychotic outbursts may be mentioned

Vascular Crises in the Eye Aside from intracerebral conditions, local vascular crises may produce disturbances of vision These local crises are traceable to spasm and embolism of the central artery of the retina

Vascular Crises in the Ear It is possible that angiospasm may play a rôle in some forms of sudden tinnitus and vertigo, but little is known about it It is a subject in which the cooperation of otologists is necessary for a better understanding

Vascular Crises in the Lungs We know comparatively little about these in man, in animals they can be induced by anaphylactic shock There is, however, a condition in the human subject that has the hall-mark of a vascular crisis, although its true pathogenesis, its morbid physiology, are but imperfectly understood I refer to acute or fulminant pulmonary edema Its chief clinical cause is myocardial disease usually associated with hypertension It is also met with in mitral stenosis and after the removal of pleural fluid by tapping Acute pulmonary edema, which has a striking tendency to recur, puts the patient's life in great peril—he may drown in his own juices While the attack endures, dyspnea, air hunger and cyanosis are very marked and the chest, back and front, is full of moist râles The patient often but not invariably expectorates quantities of clear or faintly blood-tinged sputum which coagulates on boiling

Treatment promptly instituted usually brings about speedy recovery The best measures are a hypodermic injection of morphine sulphate, gr 1/4,

and atropine sulphate, gr 1/150, venesection and dry cupping over the chest *

Whether there is a vascular as well as a bronchial spasm in asthma is as yet undetermined

Vascular Crises in the Heart From the clinical as well as from the scientific point of view, this is one of the most important phases of my subject. The whole matter culminates in the question—what is the relation of coronary spasm to angina pectoris? Personally I believe it is that of cause and effect. While other causes may be operative, perhaps in the end they act as angiospastic factors or agents. Lichtwitz⁹ believes that besides coronary spasm, angina pectoris may be produced by the failure of the physiologic dilatation during increased activity, and by the nonappearance of the increase of the circulating blood during work and under conditions of low temperature. This last circumstance may be brought about by pathologic closure of the veins of the liver and spleen whereby the blood reserve of these great reservoir organs instead of being added to the circulation is retained. This little understood mechanism, angiospastic in character, in itself does not eliminate the possibility of coronary spasm.

Vascular Crises in the Abdomen Angiospasm analogous to that supposedly at the basis of angina pectoris may occur in the abdominal vessels (angina abdominis). I have seen this in a case reported elsewhere.

Some writers attribute the gastric crises of locomotor ataxia and the colic of lead poisoning to angiospasm, a view that has much in its favor, although it may not be the whole explanation,—it hardly accounts for the obstinate constipation of lead poisoning or for the persistent, uncontrollable vomiting of tabetic crises.

Vascular Crises in the Skin Blushing and pallor of the face are vascular crises. The causes are manifold, but emotional factors seem most important.

Another dermal vascular crisis is urticaria or hives. This is a capillary crisis brought about, it is believed, by the liberation through toxic or toxico-traumatic action (bee sting, wasp sting, etc.) of histamine-like substances which act upon the smaller vessels and capillaries in such a way that fluid exudes into the perivascular tissues. Angioneurotic edema is of the same nature as urticaria. For reasons at present beyond our ken, urticaria is attended by intense itching, angioneurotic edema is not. Dermographia also belongs to the same category of skin conditions.

Vascular Crises in the Extremities It is in this special field that the subject of vascular diseases has in a short space of time won its greatest triumphs. The progress, it must be admitted, has accrued more to the advantage of diagnosis than to that of treatment, but better diagnosis is bound

* Dry cupping is best done by taking a half dozen smooth wine or whiskey glasses, moistening the inside with grain alcohol, lighting the alcohol with a match and slapping the glass on the chest, either front or back, while the alcohol is still burning. Six or eight of such cups may be applied in a few minutes. When the raised skin inside the cup begins to look purple, the cup is removed. The procedure has virtue although we do not know its *modus operandi*.

to lead eventually to better treatment The objectives of study have been in general the following

- 1 The causes of vascular disease of the extremities
- 2 The extent of the disease, i e, how far down or high up it has reached, also the type of vessel or vessels involved
- 3 The character of the disease, whether spastic, i e, functional, or organic
- 4 Treatment, which is subdivisible into
 - (a) Cure or palliation
 - (b) Arrest of the process
 - (c) Prevention of gangrene
 - (d) Treatment of gangrene

Causes of Vascular Disease of the Extremities Under this head I shall consider the principal clinical entities or syndromes in which vascular disturbances play the leading role

One of the earliest to attract attention was intermittent claudication, the symptoms of which are quite uniform The patient after walking a short distance is seized with a painful cramp in the calves that compels him to stop walking After a brief rest, from a few seconds to 10 minutes, he can proceed with ease The amount of exercise causing the cramp, as Goldsmith and Brown¹¹ have shown, is remarkably constant One of my patients experienced the cramp only on the street, he could walk about his factory all day unhindered A large proportion of sufferers have flat feet, many are heavy smokers, nearly 50 per cent of those affected are Jews of eastern origin, and, of course, the male sex preponderates greatly Examination usually shows thin, cold feet with absence of pulsation in the dorsalis pedis and posterior tibial arteries, the roentgen-ray may reveal more or less extensive calcification of the vessels

The pain in intermittent claudication is the result of a temporarily inadequate blood supply to the working muscles, but whether it is due directly to ischemia, to histanoxia, or to certain changes in the muscles has not been definitely determined The production of vasodilatation by the means now employed does not seem to have much effect on the disease, and certain tissue extracts that exert a favorable influence upon it do not seem to do so by vasodilatation

Intermittent claudication is a precursor (75 per cent) or accompaniment (98 per cent) of that terrible disease, thromboangitis obliterans As a primary disease, it occurs in later life than thromboangitis obliterans and is associated with or is dependent upon arteriosclerosis In thromboangitis, calcification of the blood vessels is rare, the process being a diffuse inflammation with thrombosis of arteries and veins In the primary form of intermittent claudication complete recovery is possible under proper treatment, the more spasm and the less sclerosis, the better the prognosis

False diagnoses are often made—rheumatism, metatarsalgia, flat feet, sciatica As regards sciatica, one should bear in mind that “bilateral

sciatica" is almost never sciatica. It may be intermittent claudication, diabetic or nephritic neuritis, cord tumor or pelvic pressure. Perhaps the most important point to bear in mind is that intermittent claudication may be an inaugural symptom of Buerger's disease.

Thromboangitis obliterans should perhaps be excluded from consideration here as it is not a vascular crisis, a functional condition, but an organic disease. However, it deserves inclusion for there is in addition to the marked structural changes a tendency to angiospasm. Naturally this is most marked in the early stages of the disease. Thromboangitis, so well described by Buerger, was at one time believed to occur almost exclusively in Russian Jews, but the great experience of the Mayo Clinic has shown that this undesirable prerogative no longer belongs to that racial group. Only one-half the thromboangitis patients seen in that clinic are Jews, the others represent all races including native American stock. It has not been observed in full-blood negroes¹². The disease occurs in men between the ages of 25 and 50 years, in the Mayo Clinic there were only six patients aged more than 60 years in a series of more than 500 cases¹³.

The cause of thromboangitis is unknown. The nature of the process suggests an infective agent but beyond that and a limited number of experiments, such as successful transplantation of resected veins the seat of phlebitis, there is no definite evidence. A second hypothesis ascribes the disease to excessive cigarette smoking. It is true that, as Barker¹⁴ has shown, the majority of patients, 91.5 per cent, who had thromboangitis obliterans used cigarettes. On the other hand, Brown¹² has observed the disease in a group of patients who never used tobacco in any form. There is no doubt, however, according to the researches of Maddock and Coller¹⁵ and of Barker¹⁴ that the smoking of cigarettes exerts a vasoconstrictor effect, and Harkavy, Hebard and Silbert¹⁶ and Sulzberger¹⁷ have demonstrated a marked skin hypersensitiveness to tobacco in patients suffering from Buerger's disease.

I shall not describe the symptomatology of the disease in its entirety, as in this article I am concerning myself chiefly with vascular crises. Angiospastic phenomena are common in thromboangitis, they result from sensory vasomotor reflexes and cause blanching and cyanosis, and a numb, dull, aching sensation on exposure to warmth. The frequency of these spastic disturbances has been the cause, as pointed out by Brown, of errors in diagnosis—Raynaud's disease being diagnosed in male patients, despite the fact that most of the patients who have Raynaud's disease belong to the female sex.

Before describing the methods of determining the vasospastic element and the location of the lesion, I shall discuss the subject of Raynaud's disease inasmuch as the same procedures are employed for its study. In fact, these procedures are now used in the investigation of all peripheral vascular disturbances, including diabetic and arteriosclerotic gangrene, embolic obstruction, and other affections hereafter to be mentioned.

Raynaud's disease has undergone hardly any changes since it was first described in 1862 by Maurice Raynaud, the man whose name it bears. The disease is a bilateral, symmetrical affection, occurring almost exclusively in women (men 5 per cent) and is characterized by intermittent attacks of changes in color, from pallid or dead-white to deep purple or black, and by trophic changes ending at times in gangrene. Additionally characteristic is the absence of occlusive lesions in the peripheral arteries. Very little is known of the etiology of Raynaud's disease. That the endocrine glands, particularly the ovaries, play a rôle, might be inferred from the preponderance of the female sex. Bernheim and Garlock (personal communication) believe that there is a disturbance in the calcium metabolism for which the parathyroids may be responsible. They have seemingly cured a number of cases by parathyroidectomy.

Scleroderma begins as an angiospastic condition, it may be preceded or accompanied by typical Raynaud's phenomena. But a mere angiospasm hardly accounts for the profound changes in the skin and subcutaneous tissues—with atrophy, adhesion and contraction of the integument—not only in the extremities but in the face, especially about the mouth, over chest and clavicles, indeed over any and all parts of the body. In a doctor's wife now under my care there is hardly an area that is not hide-bound. Severe trophic changes have occurred at the finger tips, over the digital joints, elbows and knees, and about the mouth. It is difficult to decide whether the primary process is a spastic occlusion of the vessels or whether the trophic changes, atrophy and tightening of the skin, squeeze the blood out secondarily.

Acrocyanosis is an obscure condition which affects the hands and feet, producing a bluish or reddish color and coldness. The affection is very annoying. I have seen it in two sisters, saleswomen, who were embarrassed as customers would comment on the appearance of their hands. It is most marked in cold weather but in some persons it persists even in warm weather. While resembling the asphyxial stage of Raynaud's disease, it cannot be classed with that condition as it is more permanent, especially in cold weather, and is without pain and without trophic changes. It would appear to be due to an angiospasm that reduces the capillary flow through the skin.

Erythromelalgia, a vascular disorder first described by Mitchell,¹⁸ represents a vasodilator rather than a vasoconstrictor type of disease. It has the following features: attacks of pain and burning in the extremities, with throbbing and pulsation in the arteries and arterioles and usually with redness from dilatation of the surface capillaries and venules. The condition is bilateral and is intensified by heat and by exercise, and is relieved by rest, cold and elevation. As thus defined it constitutes a clinical entity, although its cause is unknown. Symptoms resembling erythromelalgia may be met with in other diseases, in thromboangitis obliterans, in polycythemia rubra, but under such conditions it does not constitute the real disease.

The Cause of Pain in Angiospasm Perhaps the question should be put in another form why is the stopping of the blood supply to a part painful? The answer is difficult, the cause of the pain may not always or everywhere be the same. Sir Thomas Lewis explains the pain in intermittent claudication on the basis of an accumulation of metabolites in the muscles. This view is to some extent corroborated by the result obtained with injections of pancreatic tissue extract * in muscle pain of ischemic origin¹⁹. It was found that pain was relieved even though no dilatation of the vessels took place. There are, however, circumstances in which the metabolite theory would seem to be inadequate. A sudden blocking of a vein may be accompanied by violent pain as if the part had been struck. It is difficult to see how metabolites can be formed so promptly. The pain that follows the sudden closure of an artery has been attributed to a stretching of the artery proximal to the seat of closure. This would postulate a pain comparable with biliary and ureteral colic.

One of my patients suffering from polycythemia rubra was one day seized with violent pain in the left testicle. I found what seemed to be a thrombosis of the veins. Subsequently he had a similar attack about the ankle. In the case of the testicle the formation of metabolites is not likely to play an important role.

The conclusion seems warranted that the causes of pain in vascular occlusion, whether spastic or obturative, are multiple.

1 The accumulation of toxic metabolites in active tissues, especially muscles

2 *Histanoxia*, ischemia or local anoxemia

3 Pressure upon sensory nerve endings in the walls of vessels either through stretching proximal to the obstruction or through an actual squeezing of the nerve endings during spastic contraction. In either case, there would also be an inadequate blood supply to the vessel itself and to the surrounding receptor organs.

We may now take up the newer methods of determining the seat of obstruction and the presence or absence of angiospasm as an element in the ischemic process. In discussing these methods I shall borrow considerably from articles by Brown,⁸ Kramel,²⁰ Starr,²¹ Scott and Morton,²² Pearse and Morton,²³ and others.

1 *Inspection and palpation* give information of great value. Coldness up to a certain point indicates how far the circulation, direct and collateral, is inadequate. Absence of pulse in the dorsalis pedis artery is an important finding in most cases of intermittent claudication and advanced arteriosclerosis. Such absence is not infrequent in cases of coronary sclerosis.

2 *Measurement of surface temperature*, by means of delicate instruments. This is particularly useful when one wants to differentiate between angiospasm and mechanical occlusion. Readings are taken before and after nerve block. The pressor or vasoconstrictor impulses may be blocked either

* The active substance in the extracts may be adenylic acid or adenosin.

by spinal or general anesthesia or by local infiltration of the nerves to the part to be studied, or inhibited by artificial fever induced by intravenous injection of a foreign protein, e.g. typhoid vaccine. The block is normally followed by a rise of several degrees in the surface temperature, such rise being an indication that the spasm has been overcome. If there is no rise, then the obstruction of the blood vessels is not spastic but organic. Tests for the vasospastic element are of special importance in cases in which surgery is contemplated—sympathectomy, ganglionectomy or ramisectomy. If the surface temperature does not rise adequately, little can be expected from these operations.

The surface temperature of the lower extremities may also be raised reflexly by immersing the forearms and hands in warm water.⁶ Landis and Gibbon found that if the forearms are immersed for 35 minutes in water at a temperature of from 43 to 45° C, a vasodilatation is produced in the lower extremities. If the surface temperature rises to above 31.5° C significant structural disease of the arteries of the lower extremity is definitely absent. If the surface temperature fails to rise to this level, organic arterial obstruction is probably present.

3 *Oscillometry* The oscillometer determines the magnitude of pulsation of the arteries and is helpful in determining in the case of organic obstruction the point to which the circulation is adequate.

4 *Calorimetry* By determining the amount of heat loss in a given time and by skin temperature observations, calorimetric methods give indirect information of the volume flow of blood through an extremity.

5 *Histamine Test* When a minute amount of histamine is introduced into the skin a reaction occurs which Sir Thomas Lewis²⁴ and Lewis and Grant,²⁵ have classified as (1) local dilatation, (2) flare, or (3) wheal. Starr²⁶ has employed this reaction as a test for circulatory deficiency in the feet. In cases in which the circulation to the feet is impaired, the reaction to histamine is delayed, reduced or incomplete.

6 *The Roentgen-Ray* This will show calcification of the arteries if it is present, but calcification may exist with good circulation.

Visualization of the arteries by means of the injection of opaque solutions has been tried by a number of investigators.^{27 28} Allen and Camp, using a preparation of thorium dioxide called thorotrast, were able to demonstrate by means of arteriography, thromboangitis obliterans in two cases in which all other methods of examination had given inconclusive information. The attitude of the profession toward the introduction of radioactive substances into the body is distinctly one of fear. The method as employed by Allen and Camp, excellent as it is in its immediate results, will not become widely used until more is known of the effects of the prolonged presence of thorium in the body.

Treatment The vasomotor crises in the extremities, characterized as they nearly always are by pain, must be treated both causally and symptomatically. I need not discuss the causal treatment in such cases as are due

to diabetes mellitus and shall limit myself to those measures that improve or restore the circulation when it is cut off or greatly reduced through arteriospasm

To improve the peripheral circulation in vessels the seat of constrictor spasm several means are at our disposal

- 1 Alternate elevation and lowering of the limb This exercise is capable of producing a better inflow and outflow of blood It is applicable to practically all cases of obscure pains in which the cause is a local ischemia

- 2 Alternate applications of heat and cold

- 3 The use of dry heat applied by means of electric bulbs Great care must be exercised in not exposing the parts to too much heat

- 4 Alternate suction and compression in an air-tight chamber, a method, suggested by Herrmann and Reid²⁹ It is too early to speak of its value in angiospastic conditions in the limbs The limb is placed in a glass chamber and by means of a special motor air is alternately sucked out and forced in Herrmann's apparatus, called Pavaex (from Passive Vascular Exercise) and the device of Landis work on slightly different principles, but have the same underlying objectives

- 5 The injection of sodium chloride solution This is most useful in thromboangitis obliterans, it probably acts less by relieving spasms than by altering the state of the blood

- 6 The administration of calcium has been found useful in Raynaud's disease and allied conditions The dose must be fairly large, from 1/2 to 1 gram of calcium gluconate twice daily The calcium should be given an hour before meals

- 7 Acetyl beta-methylcholine chloride, commercially known as mecholine or mecholyl, has experimentally and clinically been found to cause vasodilatation Its administration is made a little difficult by the fact that it is exceedingly deliquescent The dose by mouth is 0.2 to 0.5 gram, three times a day, best dissolved in a little water and then mixed with milk It may also be given subcutaneously—never intravenously—in doses of 5 to 10 mg, to be increased up to 25 mg according to the patient's tolerance Recently Kovacs³⁰ and Doane³¹ administered it by the method of iontophoresis, which introduces the substance electrically into the limb

In some cases, especially in acrocyanosis, endocrine preparations may be useful Theelin has been tried

- 8 Parathyroidectomy in the treatment of Raynaud's disease has given encouraging results but further observations are necessary before a final judgment can be reached

I shall not go into details of the surgical operations that have been recommended for angiospastic conditions but merely mention them—sympathectomy, ganglionectomy, ramisection The usefulness of these procedures is very limited and in the case of sympathectomy the results are rarely permanent

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MULTIPLE MYELOMA ¹

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THE renewed interest in diseases of bone apparent in current medical literature had its impetus in 1926 when Mandl, in a crucial clinical experiment, established the etiologic relationship between tumor of the parathyroids and von Recklinghausen's disease of bone (osteitis fibrosa cystica). This removed the disease from the category of a morphologic to that of an etiologic entity, as demonstrated by the numerous reports of cases which followed. On the basis of both clinical and experimental study, Jaffe,¹ in his recent exhaustive review of the disease, indicates that the pathogenesis involves decalcification or demineralization of the skeletal system through the action of the increased parathyroid hormone secreted by the glandular tumor. The local bony changes are secondary to this process of resorption. The clinical features embrace the consequences of the skeletal changes and the resultant disturbed calcium metabolism.

A consideration of other conditions in which there is generalized bone destruction, especially osteoclastic carcinoma and multiple myeloma, indicates that these may simulate hyperparathyroidism. The former may lend itself to easy differentiation on the basis of a known primary cancer and characteristic roentgen-ray findings. Multiple myeloma, on the other hand, may be more difficult to differentiate. An instance of this disease which was clinically believed to represent hyperparathyroidism, with a postmortem study of the parathyroid glands, is the basis of this report.

CASE REPORT

C R, age 66, a machinist, first came under observation September 17, 1932, complaining of pain in the lower part of his back of three weeks' duration, which he ascribed to lifting an iron mold weighing about 60 pounds. The pain was dull, persistent, and much aggravated when he changed his position from sitting to standing, or on turning in bed. On further inquiry, he had also noticed loss of 30 pounds in weight and gradually increasing weakness during the previous year. The following additional information was elicited. His appetite was fair. He was troubled with frequent urination for two years, diurnal as well as nocturnal. There was no concomitant polydipsia. Constipation, which had been present for many years in mild form, had recently become more pronounced, so he resorted to enemas frequently.

Physical examination. The patient was 5 feet in height and weighed 126 pounds. He seemed normal mentally except for a slowing of his response to questions. He moved cautiously as if guarding against pain. The skin was dry, of poor texture, and showed no abnormal pigmentation. His blood pressure registered 136 systolic, 76 diastolic. On the skull was an irregular protuberance in the left occipital area due to an old injury, details of which the patient did not recall. Arcus senilis were noted, but the eyes were otherwise normal in appearance and reaction. The teeth were out and replaced by plates. The throat appeared normal, the tonsils were recessed. The

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neck showed no abnormal pulsation, no thyroid enlargement, and no adenopathy. The chest was moderately emphysematous. The lungs and heart were normal except for the distant character of the heart sounds.

The abdomen was scaphoid. No organs or masses were palpable, nor were there any tender areas. The spine was moderately kyphotic in the dorsal region. On firm pressure, tenderness was elicited over the lumbar spine and right sacroiliac joint. The extremities were extremely emaciated, and the musculature flabby. The peripheral arteries felt tortuous and sclerotic. The fingers showed Heberden nodes. The knee-jerks were present.

On the basis of the history of pain in the back with disability, loss of weight and strength, urinary frequency, and tenderness over the lower spine and pelvis, the possibility of prostatic malignancy with bony metastasis was first considered. Rectal examination revealed a small, fairly firm prostate without sufficient hardness to be considered malignant. After voluntary voiding, the patient was catheterized for residual urine. No obstruction was encountered and no urine was obtained. Roentgen-ray examination of the lumbar spine and pelvis was inconclusive, being interpreted as showing osteoarthritis of the vertebrae as well as "areas suspicious of bone destruction of the vertebrae, pelvis, and upper ends of femora."

The patient's subsequent course was one of invalidism. He was virtually bed-ridden. He remained afebrile. The pain in his back was variable, though usually made severe by motion. He continued to be troubled with constipation and urinary frequency, the latter occasionally necessitating voiding every half hour at night. His appetite became poor. He often felt nauseated and vomited once or twice daily for periods of several days.

Hospitalization was advised for further study. During a period of six days his temperature range, pulse and respiration rates were normal. Another roentgen-ray examination was done at this time and showed "marked lime deficiency in vertebrae, pelvis, femora, and ribs," as well as a marked sclerosis of the arteries. A view of the skull showed a similar type of bone involvement. The red blood cells numbered 2,870,000 and showed a moderate degree of anisocytosis, hemoglobin 47 per cent. The leukocyte count was 7450, with polymorphonuclear neutrophils 76 per cent, eosinophils 1 per cent, lymphocytes 22 per cent, and monocytes 1 per cent. The blood Wassermann and Kahn tests were negative. The urine showed a trace to one plus albumin, 20 leukocytes per high-power field, and a few hyaline and granular casts. Bence-Jones protein was not found in one test. The stool examination revealed neither blood nor parasites. The blood chemistry showed the following: Glucose 125 mg, non-protein nitrogen 49 mg, blood calcium on two estimations showed 11.8 mg and 12.6 mg as compared to a normal range of 9 to 11 mg. Two weeks later the blood calcium was 13.7 mg and the blood phosphorus 3.2 mg. A determination of urinary calcium excretion in 24 hours gave a reading of 530 mg on a diet containing approximately 200 mg of calcium, indicating the likelihood of a negative calcium balance.

It was felt that there was sufficient evidence to warrant exploration of the neck for a parathyroid tumor. At operation, however, no tumor was found, but tissue presumed to be parathyroid after study of frozen sections was removed. Post-operatively the patient was subsequently observed for signs of tetany, but none were detected, and the serum calcium showed 13.5 mg. The day following the operation cough developed, the temperature rose to 103°, the pulse rate increased, and the local chest findings indicated basal bronchopneumonia from which the patient died on the third postoperative day.

Postmortem Examination. The body was that of an extremely emaciated white male, 5 feet 3 inches in length and weighing about 100 pounds. The immediate cause of death was a generalized acute purulent bronchitis and bilateral bronchopneumonia of the lower lobes.

Inspection of the skull revealed numerous discrete, sometimes confluent, areas of resorption between the outer and inner tables. These areas were translucent, although frequently they appeared to be somewhat hemorrhagic. The texture of the skull bones did not appear to be appreciably altered. The cut edges of the bones of the skull indicated that these areas of resorption consisted of soft, somewhat hemorrhagic and gray tissue of the consistency of soft butter. The bony surfaces around these areas were excavated or concave as though they had been eroded.

The ribs and sternum were soft, occasionally brittle, easily fractured and incised. Numerous centrally located lesions of hemorrhagic character could be made out, especially upon illumination of the bones. The bone marrow appeared to be replaced by this hemorrhagic tissue, which had eroded the cortex of the bone. The bone tissue was obviously decalcified and softened. The femora, pelvic bones, tibiae, and fibulae were involved by the same type of central lesion.

A most careful dissection of the neck tissues from the base of the tongue to the

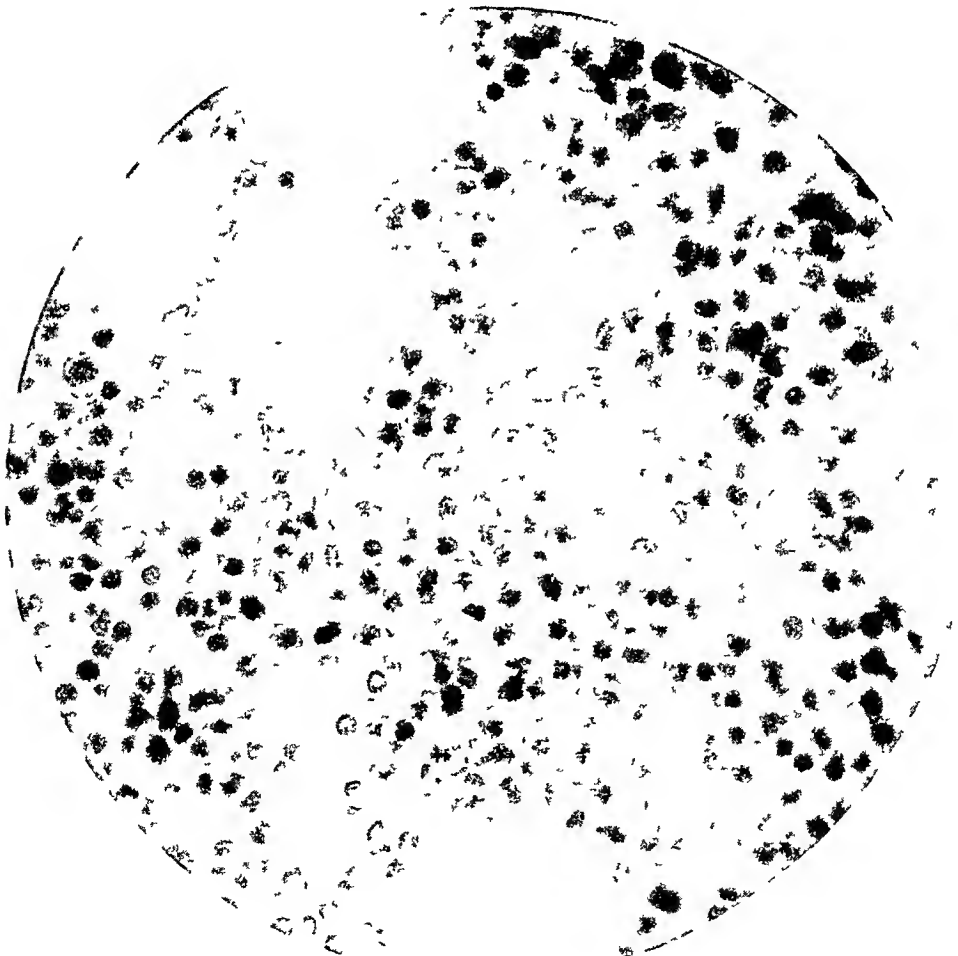


FIG 1 Bone marrow showing diffuse myelomatosis

mediastinum revealed no evidence of parathyroid tissue, nor did careful examination of thin serial sections of the thyroid

Examination of thoracic and abdominal viscera and brain did not disclose any changes other than generalized atrophy and a moderate degree of atherosclerosis. The gall-bladder contained one stone.

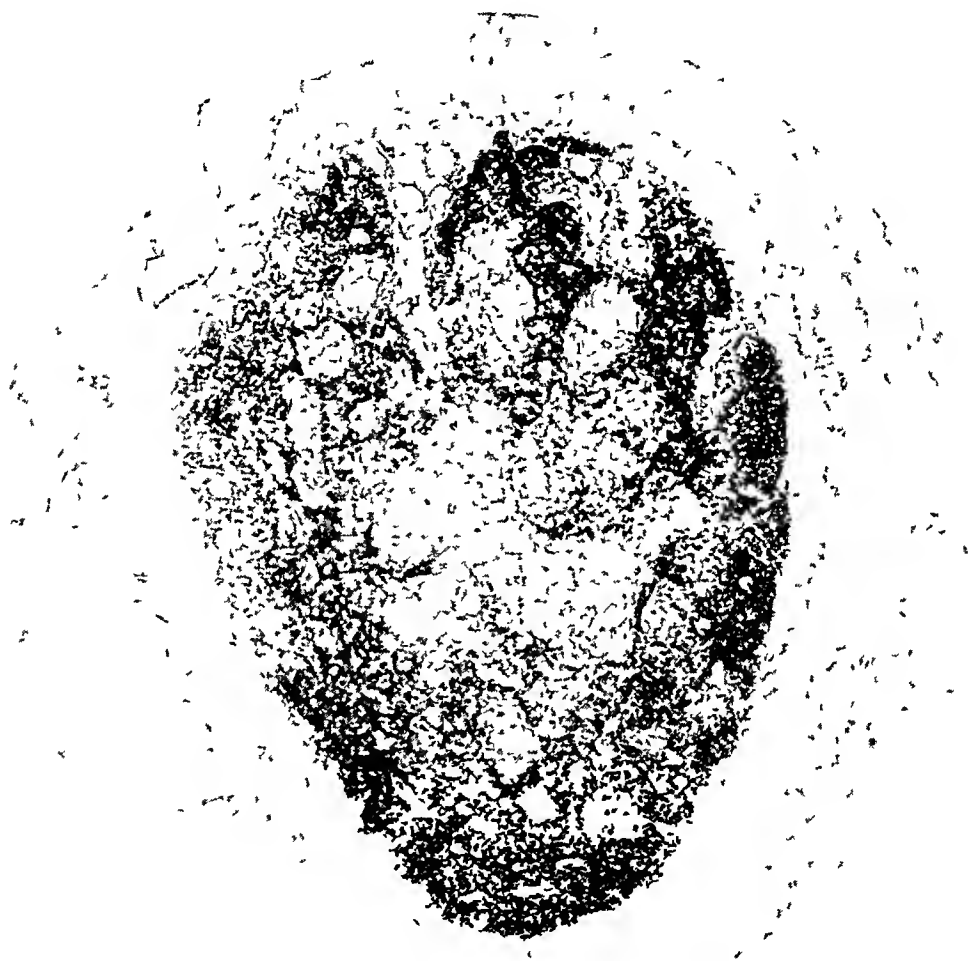


FIG 2 Low-power magnification of parathyroid gland

Microscopic examination of sections of the bones disclosed a diffuse and nodular tumor occupying the bone marrow (figure 1). The cells comprising the tumor were closely packed and remarkably uniform. The nuclei were round and usually eccentrically placed. The cytoplasm stained poorly and was homogeneous. A very occasional mitotic figure was found. Special staining revealed little or no connective tissue stroma. Small areas of atrophic fat tissue and fat cells were found between the tumor cells. Here and there between the tumor areas were moderately hyperplastic islets of myeloid tissue. These were particularly rich in erythroblasts, but the myeloid elements appeared to be normal. The bone cortex in all the bones examined

exhibited marked atrophy and consisted of slender fragments of slowly absorbing bone trabeculae. Occasional areas of recent and old hemorrhage were present in the tumor-bearing portions. Mild inflammatory reaction consisting of lymphocytes and occasional polymorphonuclears was present in the atrophic bone.

Numerous sections were made from tissue of the neck and thyroid. In one section only were we able to identify a parathyroid gland (figure 2). This was embedded in fat, and the gland itself was less in diameter than that of the low-power



FIG 3 High-power magnification of parathyroid gland

field. The gland consisted of an encapsulated mass of cuboidal cells arranged in anastomosing cords, and separated by a loose areolar tissue containing fat (figure 3). Connective tissue was scant and the vascular network difficult to make out. The cells were uniform with oval and round vesicular nuclei surrounded by clear cytoplasm. There was no evidence of hemorrhage nor inflammatory reaction. The final diagnosis was generalized myelomatosis.

Two aspects of this case merit further elaboration the relation of the parathyroid glands to multiple myeloma, and the similarity between the clinical features of this disease and hyperparathyroidism. Our interest was aroused in this instance by the absence of parathyroid tissue except as found in the microscopic sections. While it is appreciated that the glands may be situated in other than their usual sites, the dissection in this case was so thorough that the possibility of our having overlooked abnormally located glands is unlikely. Whether or not the glands in this patient were atrophic beyond that which is occasionally encountered in individuals of his age may reasonably allow for difference of opinion, but the case does indicate the compatibility of the absence of parathyroid hyperplasia with myelomatosis. Theoretically, it may be suggested that the glands are either unaffected by the disease, or undergo atrophy. To assume that because of the abnormal mobilization of calcium from the "skeletal storehouse," the parathyroids in this case were thrown into a functional, and later, into an anatomical atrophy, is as reasonable as the assumption that hyperplasia of the glands may be stimulated by the same process.

The latter conclusion was drawn by Bulger and Bair² from a case strikingly similar to ours, but considered clinically to have neoplastic disease of the bones. The serum calcium in their case was 16 mg and phosphorus 3.7 mg. At necropsy myelomata of the plasma cell type were found in the vertebrae, ribs and clavicles, as well as metastatic calcification in the lungs, stomach mucosa, and kidneys. In three parathyroid glands definite hyperplasia was found. On the basis of their findings in this case, they presumed the existence of a state of "secondary hyperparathyroidism" due to hyperfunctioning of the parathyroid glands. They concluded that "many generalized diseases of bones accompanied by extensive absorption or destruction of bone substance, lead eventually to significant parathyroid hyperplasia." A different conception was held by Klemperer³ who, in a case of skeletal carcinomatosis showing newly formed but uncalcified osteoid tissue, found a tumor of one of the parathyroid glands. He interpreted the hyperplasia as the structural expression of an inadequately functioning gland. In other cases of myeloma, Jores⁴ and Peters⁵ did not find any changes in the parathyroids. Jaffe¹ holds to the theory of a "compensatory reaction" as accounting for the enlargement of the glands in diseases other than von Recklinghausen's. He indicates that the pathogenesis or mechanism of such enlargement is not obvious, but he considers that it may be an attempt on the part of the glands to maintain a quantitative increase of the hormone to counteract the effect of calcium deprivations in these conditions. From these divergent views it may be concluded for the present at least, that anatomical hyperplasia or functional hyperactivity of the parathyroid as the result of disturbances of calcium metabolism due to intrinsic disease of bone, is not proved.

On the basis of their clinical features, and because of like alterations in

the calcium metabolism, Jores¹ was among the first to call attention to the similarity between multiple myeloma and hyperparathyroidism. He reported his findings in two instances of myeloma, with studies of the calcium balance, and emphasized the negative balance as in hyperparathyroidism. More recently, Caylor and Nickel⁶ attest to the diagnostic difficulty encountered in a case of generalized osteoporosis with hypercalcemia in which the diagnosis of myeloma was finally based on a rib biopsy. That hypercalcemia may occur in myeloma is a long known fact, but that it may be absent in hyperparathyroidism has also recently been shown. Wilde⁷ and Gutman⁸ have reported cases in which the serum calcium was normal or only slightly increased in this disease. The presence of the Bence-Jones albumose in myeloma is neither a constant nor a pathognomonic feature. While the roentgenologic findings in the bones differ in the two diseases, it is significant that in the case above reported, a competent roentgenologist believed the lesions represented decalcification due to parathyroid overactivity. It becomes evident that one or two diagnostic procedures will yield insufficient information in a case belonging in this group of diseases, and that conclusions should be drawn only from comprehensive clinical, chemical, metabolic (calcium balance), roentgen-ray, and biopsy studies. This is all-important in the event of the possible discovery of hyperparathyroidism in its early phases with a chance for cure by surgical removal of a parathyroid tumor.

The clinical history and physical examination may yield important clues pointing to a direct diagnosis. While pain in various regions of the skeletal system, loss of weight and strength, gastrointestinal and urinary symptoms, muscular wasting, and spontaneous fracture are common to these diseases, the finding of a small tumor in the thyroid region should at once lead to a consideration of a parathyroid adenoma and warrant exploration if substantiated by the results of other examinations. The quantitative changes in certain of the blood serum constituents constitute the most important features in these conditions. In most cases of hyperparathyroidism there is a variable hypercalcemia usually in association with a normal or low level of serum phosphorus. The significance of a normal serum calcium, however, has been alluded to above. On the other hand, in many cases of myelomatosis the calcium level is appreciably elevated, although the phosphorus level is generally normal or slightly elevated. More recently an increase in the amount of the serum protein has been reported in cases of multiple myeloma by Wintrobe and Buell,⁹ and by Reimann,¹⁰ with the suggestion that this factor is intimately related to the nature of the disease. The globulin fraction, according to Peters,² is especially involved and it is in this disease in which it may show its greatest increase. The determination of the serum phosphatase, according to the method of Bodansky,¹¹ will yield increased values in hyperparathyroidism and normal values in myeloma.

From the standpoint of the calcium metabolism alone, the two conditions

herein considered are highly similar, both showing increased calcium excretion in the urine. In ordinary clinical work, studies of calcium balance with measured intake and output in urine and feces are not easily applicable. The diet suggested by Snapper¹² facilitates such a study when desired, since it entails only a determination of the calcium excreted by the kidneys.

The bone changes disclosed by roentgen-ray examination in these diseases may at times bear striking resemblances, depending on the degree of development of the disease. Camp¹³ has recently delineated the characteristic changes in hyperparathyroidism. Confronted with roentgenograms presenting only a state of generalized osteoporosis, a differentiation is not readily made unless there be changes in the nature of cysts and giant cell tumors indicative of advanced von Recklinghausen's disease.

As a final and conclusive diagnostic procedure, biopsy of bone, either of rib, iliac crest, or by sternal puncture, as suggested by Custer,¹⁴ may be resorted to in any case when indicated because of equivocal results yielded by other laboratory procedures.

SUMMARY

A case report of multiple myeloma with clinical and laboratory features simulating hyperparathyroidism is presented. The possible rôle of the parathyroid glands in myelomatosis and other generalized bone disease is considered. In the case reported, parathyroid atrophy was encountered, and the concept of secondary or functional hyperparathyroidism is questioned. The similarity between myelomatosis and hyperparathyroidism appears to be on the basis of disturbed calcium balance common to both. The laboratory methods for differentiating between the two diseases are enumerated.

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HYPERPROTEINEMIA, AUTOHEMAGGLUTINATION, RENAL INSUFFICIENCY AND ABNORMAL BLEEDING IN MULTIPLE MYELOMA ¹

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MULTIPLE myeloma cases notoriously present bizarre clinical syndromes often diagnosed as arthritis, neuritis, severe anemias, or chronic nephritis, etc., depending on the predominance of various symptoms or findings such as pain, pallor, or urinary or blood nitrogen findings respectively.

Likewise many unique chemical and hematological findings are reported, most of which are neither entirely explained nor satisfactorily related to the underlying disorder. Reimann,¹ however, first called attention to the cause of the autohemagglutination seen in the blood of a patient who had been treated for arthritis for months. The fact that this patient's red cells formed tight rouleaux in smears and in a red cell pipette when Hayem's solution was used as a diluent, led him to suspect hyperproteinemia and, as a cause for this, multiple myeloma. His impression was correct as was proved at autopsy. Reimann rightly distinguishes autohemagglutination (marked rouleau formation) from true isoagglutination which is used in typing bloods for transfusions, although in the former clumps of great size may be formed which are distinguished with difficulty from clumps due to isoagglutinations. Bonniger² reports similar rouleau formation in smears and difficulty in counting red cells because of a precipitate forming with Hayem's solution, but not with salt solution. Serum from his patient still formed a precipitate, even when diluted 10 times. Both the above authors report marked clumping of donors' blood cells, when the serums of their patients were mixed with cells from various donors of the same isoagglutinin group, while the patients' red cells were not affected by serum of the same group. The sedimentation rate of the erythrocytes in Reimann's case was so rapid that complete settling had occurred in 10 minutes, and large macroscopically visible clumps were seen within the sedimentation period. Freund and Magnus-Levy³ report six cases in the literature, including one of their own, in which the sedimentation rate was very rapid, and Bonniger's case showed the same phenomenon. Reimann, Bonniger, Freund and Magnus-Levy ascribe the rapid rate to the marked rouleau formation, and this in turn to the increase in the blood globulin and fibrinogen in their cases. Fahraeus⁴ has proved the same in bloods of patients with various diseases by means of preparations of bloods and blood proteins in the test tube, and explains the rouleau formation as due to changes in the interface between

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TABLE I
Summary of Cases in Literature Showing Hyperproteinemia

| Author | Year | Total Protein | Albumin | Globulin | Fibrin | Bence-Jones in Blood | Renal Insufficiency | Bence-Jones in Urine | Blood Calcium | Blood Phosphorus | Autohem- agglutination | Increased Sedimentation Rates | Red Cells in Millions | Reference |
|--|--------------------------------------|---|--------------------------------------|---------------------------------------|----------------------|-------------------------|------------------------|-------------------------|---------------|---------------------|---------------------------|-------------------------------------|--------------------------|---|
| Jacobson, V. C. | 1917 | High | | | | 7.86% | Severe | 0.7% | | | | | 238 | Jr. Urol., 1917, 1, 167 |
| Pittman, H. | 1925 | 8.7 | | | | | Slight | 4.5% | | | | | | Med. Klin., 1925, xxi, 368 |
| Perlman, W. A. Delrue, G., and Geschickter, C. | 1928 | 12.32 13.40 13.84 | 1.42 1.67 4.06 | 10.11 11.04 9.09 | 0.79 0.69 0.69 | trace trace trace | | + | 10.8 | 4.8 | | | 180 | Jr. Am. Med. Assoc., 1928, xc, 755 |
| Bunnick, E. G., and Greene, C. H. (Case 2, Case 13) | 1929 1929 | 9.00 10.54 | 2.50 4.45 | 6.50 6.09 | | + | ++ Slight | ++ | | | | | 183 360 | Arch. Int. Med., 1929, xlv, 486 |
| Hubbard, R. S. | 1930 | 8.94 | 5.56 | 1.74 | 0.79 | | | 13 gm. | | | | | | Jr. Lab. and Clin. Med., 1930, xv, 554 |
| Bennhold, H. (Case a, Case b, Case c, Case e, Case f) | 1931 1931 1931 1931 1931 | 11.40 9.50 8.00 16.00 14.00 | 1.80 2.60 3.60 1.20 6.20 | 9.60 6.90 4.40 14.80 7.90 | | | | | | | | | | Personal communications to Freund, R., and Magnus-Levy, A. Ztschr. f. klin. Med., 1932, cxvi, 1 |

TABLE I—(Continued)

| Author | Year | Total Protein | Albumin | Globulin | Fibrin | Bence-Jones in Blood | Renal Insufficiency | Bence-Jones in Urine | Blood Calcium | Blood Phosphorus | Autohem- agglutination | Increased Sedimentation Rates | Red Cells in Millions | Reference |
|--|--------------|----------------|--------------|---------------|--------|-------------------------|------------------------|-------------------------|---------------|---------------------|---------------------------|-------------------------------------|--------------------------|---|
| Jores, A | 1931 | 9.30 | 3.30 | 5.80 | 0.19 | | | + | 18.0 20.0 | 3.47 4.04 | | ++++ | | Klin Wchnschr, 1931, x, 2352 |
| Reimann, H | 1932 | 10.12 | 0.90 | 3.84 | 5.48 | | Slight | 0 | 18.0 | | ++++ | ++++ | 3.10 | Jr. Am Med Assoc, 1932, xcix, 1411 |
| Medes, G | 1932 | 16.00 | | | | | | | | | | | | Personal communication to Reimann |
| Shurer, J W, Dun- can, W, and Haden, R L (Case 2) | 1933 1933 | 13.78 11.37 | 2.44 2.44 | 11.34 8.93 | | 7.85% 4.14% | +++ 0 | 0 + | 14.1 | | | | 3.24 2.84 | Arch Int Med, 1932, l, 829 |
| Bonniger, M | 1933 | 13.00 | | | | 0 | | 0 | | | ++++ | ++++ | | Deutsch med Wchnschr, May, 1933, lx, 770 |
| Wintrobe, M M and Buell, M | 1933 | 11.90 | 2.50 | ? | | ? | | | | | | | 3.29 | Bull Johns Hopkins Hosp, 1933, lvi, 156 |

the red cells and the blood serum, either by reducing the relative electric charge or by depriving the surface colloids of water

In the literature relatively few references to the amount of blood proteins in multiple myeloma are found. Eighteen cases are found showing hyperproteinemia (total protein eight grams or over per 100 c c serum or plasma) (See table 1). Freund and Magnus-Levy found that in about half of the 23 cases collected by them in which blood proteins were determined, figures higher than normal were found, and since then a case is reported by Barker⁵ having a normal protein content. It is interesting to note (table 1) that in the cases showing hyperproteinemia the Bence-Jones protein output in the urine was absent or slight, and that, as Freund and Magnus-Levy point out, cases passing much Bence-Jones protein in the urine show low or normal total blood protein. The table also shows that the increase in serum protein is nearly always due to an increase of the globulin fraction, although Reimann's case showed a marked increase of fibrin.

In cases where the partition of the increased globulin has been studied, the euglobulin has been found to form the largest part of the globulin (Perlzweig, Delrue and Geschickter,⁶ Bannick and Greene,⁷ Reimann,² Shurer, Duncan and Haden⁸). Freund and Magnus-Levy also report an extramedullary plasmoma with a normal total protein (7.3 grams) but there was a reduction of albumin to 3.6, and increased globulin to 3.7 grams. Marked increase in fibrin was present, also a very rapid sedimentation rate.

High serum protein values are extremely rarely found in other diseases. In severe dehydration the figures found in multiple myeloma are approached, and also in Kala azar in which Wu⁹ found the highest figure 10.5 per cent total protein in one case and in this and other cases a marked increase in globulin as high as 7 per cent was found. Rowe¹⁰ found 10.4 per cent total protein in a case of undiagnosed enlargement of the inguinal lymph nodes after long venous stasis, the highest in a large series of various diseases, and Loeper et al.¹¹ found 11 grams in a case of a malignant tumor of the kidney. In a very peculiar case of osteopathia osteopriva in a senile person, Reiche¹² found 11.4 grams total protein with 8.6 grams of globulin.

Jacobson,¹³ and Shurer, Duncan and Haden⁸ found a large quantity of protein which precipitated at 56° C. which they considered to be Bence-Jones protein, but Magnus-Levy, Perlzweig,⁶ and Wintrobe and Buell¹⁴ believe that this is not proved, since highly unstable euglobulin may be precipitated also. Wintrobe and Buell call attention to the fact that the temperature of precipitation and solution of a protein are not physical chemical constants for these are influenced by many factors such as the concentration of the protein itself, the hydrogen-ion concentration, and the quantity of the electrolytes and other substances present, such as urea. In the two cases of Shurer, Duncan and Haden, however, the protein coagulable at 56° C., after washing thoroughly, redissolved in water on boiling. Perhaps some of the discrepancies in the literature can be explained on the assumptions of Wintrobe and Buell that Bence-Jones protein is not a single chemical individual.

but is a class of substances which exhibit a peculiar coagulation phenomenon, and that other influences such as mentioned above may determine the presence or absence of a precipitate at any given temperature. Similarly, Bennhold¹¹ states that the normal proteins of serum are not sharply divided but that as one increases the quantity of ammonium sulphate in salting out experiments, increasing amounts of precipitate result. In 21 other cases besides those in table 1, namely Weinberg and Schwarz¹⁶ (three cases), Citron,¹⁷ Short and Crawford,¹⁸ Bannick and Greene⁷ (three cases, including two of Walters), Mainzer,¹⁹ Freund and Magnus-Levy (two cases), Ellinger,²⁰ Gabbe,²¹ Zadek and Lichtenstem,²² Abderhalden,²³ Hewitt,²⁴ d'Alloco,²⁵ Decastello,²⁶ Donetti,²⁷ Marcovici,²⁸ Karlins and Lundquist,⁹ protein coagulating at 56° C has been reported. Freund and Magnus-Levy believe that many of these precipitates are due to fibrinogen and not to Bence-Jones protein.

Two cases showing much more bizarre findings are reported by Wintrobe and Buell,¹⁴ and Karlins and Lundquist. In the plasma of the first case, in a hematocrit a layer of dense yellow precipitate one cm high was found, composed microscopically of brown masses varying in size and appearing very viscid. When the tube was put on the ice overnight a cloudy white precipitate occurred throughout the plasma. This disappeared on exposure to room temperature and reappeared on cooling. This precipitate after purification was coagulated in faintly acid solutions at 40° C but did not disappear on boiling. Complete fractionation of the proteins of this plasma was not possible because of the spontaneous precipitation. Karlins and Lundquist's case showed a fine milky precipitate just above the layer of blood cells, almost equal in volume to the blood cells when blood was treated with trichloroacetic acid. When this precipitate was washed thoroughly and heated with water, complete solution of the material occurred, but then it did not reappear on cooling. It precipitated, however, on adding sulphosalicylic acid, disappeared on boiling and reappeared on cooling.

For many years much dispute has arisen as to the cause of the renal insufficiency found in many cases of multiple myeloma. Various pathological descriptions of the kidney are recorded, oftentimes far from explaining the azotemia satisfactorily. In a recent article Bell³⁰ has summarized most of the cases in the literature in which renal changes are mentioned and he concludes that in some the impairment has been due to arteriosclerotic changes, pyelonephritis, or prostatic hypertrophy. Other cases, including most of his own, showed as the only direct effect of multiple myeloma, formation of tubular casts of Bence-Jones protein which occluded the tubules and led to tubular atrophy. When large numbers were occluded, extensive atrophy of the cortex and renal insufficiency ensued. In one case furnished him by me (Case 3 of the series below) he concluded that the renal insufficiency was apparently caused by the accumulation of a highly concentrated protein in the glomerular capillaries, and in two other instances the same appearance was found in a few capillaries. This observation has never been mentioned

in other reports. In Bell's report the cases showing the atrophy due to tubular occlusions by casts and the case of Mainzer were those in which large amounts of Bence-Jones protein were excreted.

Abnormal bleeding and clotting seem to be uncommon in this disease in spite of the marked involvement of the bone marrow. Of all the reports reviewed for this article the only case in which this phenomenon occurred is in the one reported by Wintrobe and Buell who mention prolonged bleeding time, and that the blood did not clot properly. At this time their patient's platelets numbered 108,000, whereas some time previously the platelet count had been 146,000. Citron, Perlzweig et al., and Reimann, report that only a very small amount of serum was expressed by the clot, and sufficient fluid for analysis could be obtained only by mechanical pressure of the clot. Citron's case and one of Freund and Magnus-Levy showed extremely prompt clotting, so that preparations for counting cells could not be made or were made with difficulty.

The following four cases represent the last four consecutive myeloma patients seen by the author. They show most of the queer clinical and chemical findings mentioned above.

CASE I

W. C., male, forest ranger, age 44, was first seen by Dr. R. W. Kraft on November 27, 1933 complaining of pain in the lower portion of his back, and marked loss of strength and color, dating back to the latter part of June 1933, from which time the symptoms had become progressively worse. By September of the same year he was markedly anemic and had to rest after walking a block or less and any exertion made him dyspneic and produced dull pain in his legs. After a few minutes' rest the pain in the legs would disappear and he would feel fairly comfortable. About November 15, 1933 a strenuous automobile ride over rough roads was followed by severe pain in the lower dorsal region of his spine. The pain had been continuous until he was admitted to the Pasadena Hospital on December 11, 1933. There were no other complaints worthy of mention.

On examination he was well nourished, markedly pale, the pulse was 90, respiration and temperature and blood pressure normal. There was a faint systolic murmur (hemic?) heard at the base of the heart. The lungs were clear. The abdomen showed no masses or tenderness and the spleen and liver were not palpable. The prostate was not remarkable. There was slight tenderness over the sixth dorsal spine. The lymph nodes throughout the body were not enlarged and there were no swellings noted on any of the bones. No edema was present.

The blood counts are given in table 2. The red cells were on the average slightly smaller than normal and varied slightly in size and shape, some were well filled with hemoglobin while others were moderately pale. Some of the polymorphonuclear leukocytes showed toxic granulation. On all smears occasional immature granulocytes were seen as well as a few normoblasts and rarely a megaloblast. The smears showed also marked rouleau formation of the red cells (figure 1A) even in the thin portions and wet films of oxalated blood showed large clumps of erythrocytes (figure 2A). Grossly visible clumps of red cells occurred in a sedimentation tube, and within 10 minutes the entire column of red cells had settled completely. The patient's serum caused marked clumping (figure 2B) primarily due to profound rouleau formation with several suspensions of red cells from donors of the same blood group as the

TABLE II
Hematologic Studies in Cases Reported in Text

| | Date | Hb % | Reds in millions | Whites in thousands | Myeloblasts | Promyelocytes | Myelocytes | Polymorpho-nuclears | | | Eosinophiles | Basophiles | Monocytes | Lymphocytes | Plasma cells | Platelets in thousands | Venous clotting time (10 mm tube) | Venous clotting time normal control | Bleeding time (Duke's method) | Prothrombin time | Prothrombin time normal control | Clumping in Hayem's solution |
|---------------|----------|------|------------------|---------------------|-------------|---------------|------------|---------------------|-------------|-----------|--------------|------------|-----------|-------------|--------------|------------------------|-----------------------------------|-------------------------------------|-------------------------------|------------------|---------------------------------|------------------------------|
| | | | | | | | | Juveniles | Stiff forms | Segmented | | | | | | | | | | | | |
| Case 1, W C | 11-27-33 | 20.7 | 1 280 | 3.9 | 2 | 2 | 1 | 6 | 8½ | 41½ | 1 | 0 | 9 | 28½ | 1 | | | | 10' | | | 0 |
| | 12-11-33 | 20.5 | 1 050 | 7.2 | 1 | 1½ | 1 | 1 | 6 | 51 | 0 | 0 | 6 | 33 | 0 | red | 91' | 32' | 6' | | | 0 |
| | 1-3-34 | 38.5 | 2 225 | 4.5 | 1 | 0 | 1 | 1 | 6 | 35 | 2 | 0 | 15 | 33 | 3 | | | | 5' | | | 0 |
| | 2-21-34 | 32.8 | 1 810 | 4.0 | 4 | 1 | 1 | 3 | 11 | 17 | 15 | 1 | 17 | 27 | 3 | 140 | 46' | 41' | 5' | | | 0 |
| Case 2, J C | 2-8-34 | 40.0 | 1 960 | 3.2 | 1 | 1½ | 2 | 1 | 5 | 43 | 0 | 0 | 3 | 42 | 2 | 98 | 330' | 25 | 30+ | | | 0 |
| Case 3, J McM | 11-9-31 | 34.7 | 2 040 | 6.5 | 0 | 0 | 0 | 1 | 76 | | 0 | 0 | 4 | 19 | 0 | 298 | 140' | 22' | 30+ | 13' | 5' | + |
| Case 4, M C | 9-24-28 | 17.0 | 1 620 | 5.6 | 0 | 0 | 2 | | tot 48 | | 0 | 0 | 3 | 47 | 0 | 0 | | | | | | + |
| | 10-2-28 | 32.0 | 1 810 | 6.0 | 0 | 0 | 1 | | tot 50 | | 1 | 0 | 5 | 43 | 0 | 90 | | | | | | + |
| | 10-28-28 | 29.0 | 1 780 | 6.3 | 0 | 0 | 3 | | tot 55 | | 1 | 0 | 5 | 36 | 0 | 160 | | | | | | + |
| | 11-12-28 | 32.0 | 1 510 | 5.0 | 0 | 0 | rare | | tot 68 | | rare | 0 | 1 | 31 | 0 | 64 | | | | | | + |

patient (Group IV Moss) This phenomenon was present at dilutions of one to four but not at one to eight of the patient's serum, at which dilution the serum was capable of causing isoagglutination of Type II and Type III cells. As noted in table 2, there was a marked delay in the clotting time of the venous blood and at one time

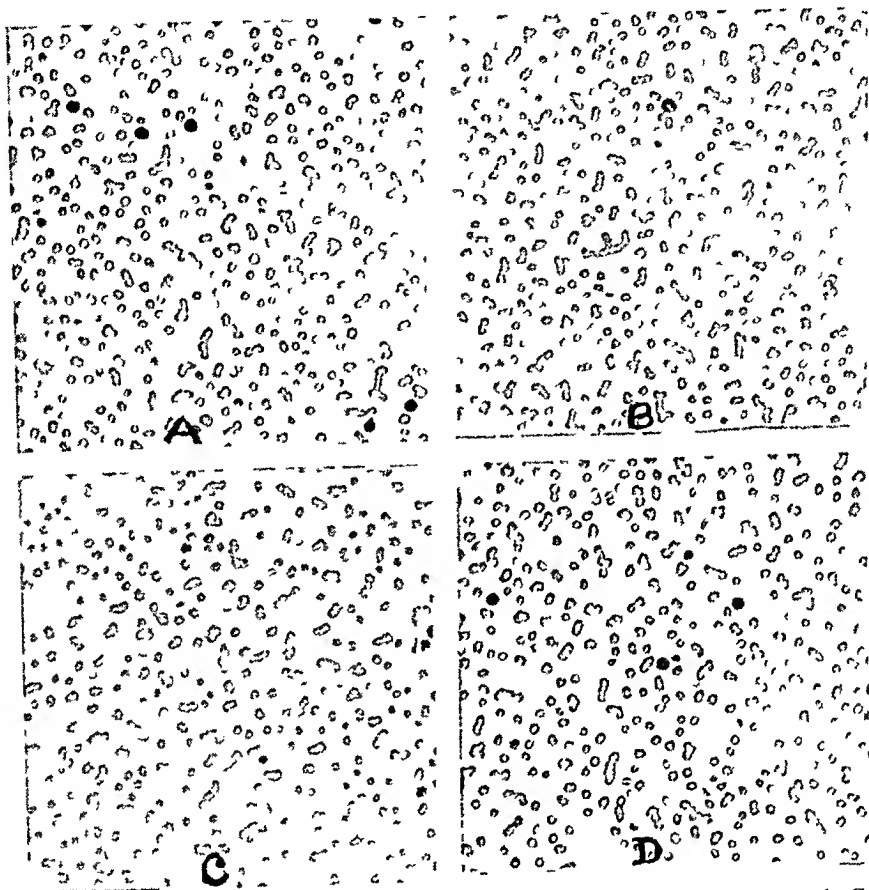


FIG 1 Wright stained smears of blood, showing marked rouleau formation A Case 1 B Case 2 C Case 3 D Case 4

moderate increase in bleeding time. There was no coagulation of blood serum at 56 or 60° C for an hour in a water bath. At about 70° slight clouding occurred in the tube, as well as in one containing serum from a normal person. Bence-Jones protein was therefore considered to be absent from the blood serum. Numerous samples of urine, about 12 in all, were tested for the presence of Bence-Jones protein, and none was demonstrated. Only occasionally was a trace of albumin found and on occasions a few granular and hyaline casts. Specific gravity varied from 1.015 to 1.026. Blood chemistry reports are given in table 3. There was marked increase in protein, due largely to an increase in globulin and about one and one-half to two times the normal fibrin was present. A marked increase in uric acid without change in the non-protein-nitrogen was also seen. Also, a moderate increase in blood calcium was demonstrated. The possible diagnosis of multiple myeloma was suggested, roentgen-rays were taken on December 19, 1933 and showed numerous closely packed areas of diminished density involving the entire cranial vault and some of the upper

ribs The largest of these areas was less than one cm in diameter and most were considerably less There was moderate collapse of the sixth dorsal vertebra There

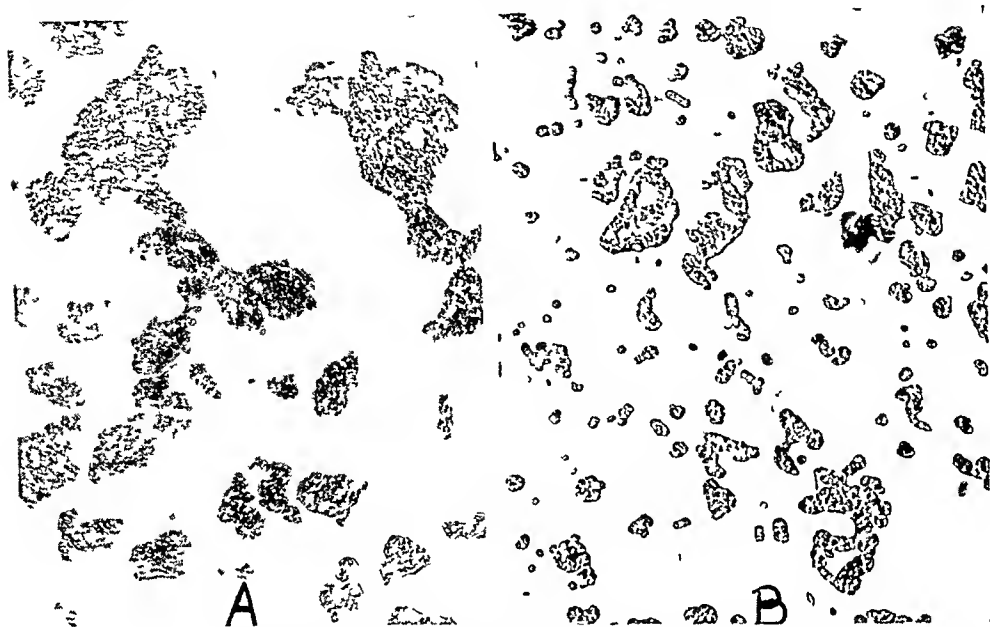


FIG 2 Case 1 *A* Wet film of oxalated blood of patient showing profound hemagglutination *B* Wet film of red cells of compatible donor plus patient's serum diluted 1 to 4, showing marked hemagglutination

was no convincing evidence of any involvement of the long bones of the extremities The findings were reported as being consistent with multiple myeloma

A bone marrow puncture was made in the upper part of the sternum on December 18, 1933 and smears and sections of the gray-red fleshy fragments received showed

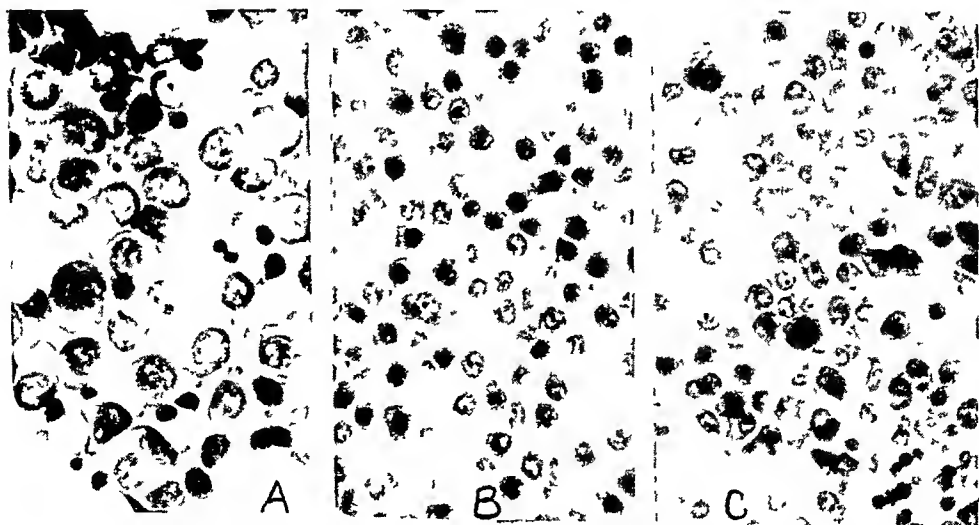


FIG 3 *A* Wright stained smear of marrow from sternum of Case 1, showing typical plasma cells *B* Section of myeloma from vertebra (Case 2) showing plasma cells *C* Section of marrow from femur of Case 3, showing plasma cells

TABLE III

Blood Chemistry in Cases Reported in Text

| | Date | Grams per 100 c.c. plasma | | | | Milligrams per 100 c.c. of blood | | | | | CO ₂ Volume % | Milligrams per 100 c.c. of serum | |
|-------------|----------|---------------------------|---------|----------|--------|----------------------------------|-----------|------------|-------|-------------------------|--------------------------|----------------------------------|------------|
| | | Total Protein | Albumin | Globulin | Fibrin | Non-Protein Nitrogen | Uric Acid | Creatinine | Sugar | Chlorides (Whole Blood) | | Calcium | Phosphorus |
| Case 1, W C | 12-19-33 | 13.2 | 4.3 | 8.30 | 0.60 | 33.3 | 4.3 | 1.7 | 115 | 430 | 47% | 12.6 | 4.6 |
| | 2-21-34 | 10.8 | 4.2 | 6.18 | 0.42 | 31.6 | 8.8 | 1.8 | 124 | 530 | 49% | 12.2 | 3.6 |
| | 5-10-34 | 10.8 | 3.4 | 7.10 | 0.30 | 32.0 | 10.0 | 1.6 | 101 | 530 | | 12.0 | 3.1 |
| Case 2, J C | 2- 5-34 | 15.0 | 5.5 | 8.80 | | 160 | 12.0 | 5.5 | 133 | 524 | 48% | 20.0 | |
| Case 3, J M | 11-11-31 | | | | | 100 | 4.0 | 2.9 | 111 | 509 | 45% | | |
| | 11-16-31 | | | | 0.410 | 200 | 10.0 | 5.0 | | | | | |
| Case 4, M C | 9-20-28 | | | | | Urea N 14.0 | 5.16 | 2.5 | | Phasma Chlor | | | |
| | 10- 2-28 | 11.37 | 1.86 | 9.51 | | 25.4 | | | | | | | |
| | 10-13-28 | 11.51 | 1.57 | 9.94 | | | | | | | | | |
| | 10-26-28 | | | | | 35.6 | | 2.46 | 126 | 680 | | | |
| | 11- 5-28 | 13.21 | | | | | | | | | | | |
| | 11-10-28 | | | | | 27.3 | | | | 640 | | | |

a more or less diffuse growth through the marrow of plasma cells (figure 3A) Typical eccentric nuclei which were nearly spherical were seen and typical clumping of chromatin noted in many, producing a "watch-face" appearance. Many were obviously immature and in these the chromatin was more diffusely spread through the nucleus. These cells had replaced most of the normal bone marrow cells and by count fully 80 per cent of the cells were plasma cell types. The diagnosis of "plasma cell myeloma" was made.

On May 11, 1934, firm pressure was applied to the eyeball while the retinal vessels were studied with the ophthalmoscope. When the pressure was sufficient to stop the circulation in the arteries, the venous flow was very sluggish, and large red granules slowly following one another along the course of the veins were seen, resembling the aggregates seen in the sedimentation tubes. Without pressure this phenomenon could not be seen. It was not present in the eye of the author. The observations, first made by Dr. L. L. Henninger, were verified by Dr. George Dock who saw this patient several times in consultation, and myself.

The patient was given several transfusions and was allowed to be up and around with a leather support for his back. Deep roentgen-ray therapy was given over the spine and he was free from pain thereafter. About the middle of March he noticed some difficulty in locomotion and was put to bed with a back brace, and after a few weeks was allowed to get up gradually. Several transfusions were given which increased his blood hemoglobin and red cells temporarily, but within a period of two weeks following each transfusion, the blood had slumped to its previous level. He was discharged from the hospital unimproved on May 12, 1934.

CASE II

J. C., male, age 68, was first seen in the office of Dr. H. B. Rickabaugh on January 11, 1934, complaining of severe pain in the right hip and in the lower part of the back, which was first noticed by the patient two months previously and had become progressively worse. Slight pain was also felt in the right side of the chest. He had also some loss of weight and strength. There were no other complaints. His family and past history revealed nothing of interest, except that he had suffered from some backache for three years.

Physical examination revealed an elderly man, fairly well nourished but showing a moderate pallor. There was marked pyorrhea but otherwise the head and neck were negative. The heart was not enlarged, but the tones were somewhat feebler than normal. Examination of the lungs was negative. The abdomen showed no masses, distention or noteworthy tenderness. The liver and spleen were not palpable. There was tenderness on firm pressure over the lumbar vertebrae and in the region of the right hip and along the upper portion of the course of the right sciatic nerve. There was no edema. The pulse, temperature and respiration were normal and the blood pressure was 108/80. The blood examination showed 45 per cent hemoglobin, 2,500,000 red cells and 5,400 white cells. The diagnosis of a rheumatoid infection was made and the patient treated by diathermy at the office, and symptomatically. On February 1, 1934 constant oozing from the gums began, which could not be stopped, and the patient was sent to the Alhambra Hospital. A transfusion of 500 c.c. of blood was given, but the bleeding continued.

Several urine samples showed specific gravity of about 1.015, protein +, sugar negative, and many hyaline and finely and coarsely granular casts, a few leukocytes and renal epithelial cells, but no red cells. A faint trace of Bence-Jones protein was demonstrated by acetic acid, sodium chloride and heat test, and by Exton's sulphosalicylic acid reagent. Most of the protein was serum protein which did not dissolve on boiling, but the Bence-Jones protein did, and after the coagulated serum protein was filtered off while still hot a faint cloudiness occurred on cooling. The amount was so small that it might have been missed easily if not carefully searched for.

The hematological studies conducted at the hospital are partly included in table 2. The red cells showed marked rouleau formation, even in thin parts of properly made smears (figure 1B). There were no noteworthy changes in the individual red cells except for rare polychromatophilic cells. A few of the neutrophils showed toxic granulation. The platelets were normal. Wet films of fresh and oxalated blood showed marked clumping, exaggerated rouleau formation, and the clumps could be broken by pressure on the cover glass only to reappear immediately after the agitation was stopped. Grossly visible cayenne pepper-like clumps of red cells were formed within one minute after setting up a 200 mm sedimentation tube, and within 15 minutes sedimentation was complete. There was marked prolongation of clotting time to five and a half hours in a 10 mm paraffined tube. The cells settled promptly and the supernatant fluid formed a jelly-like mass which did not contract in 48 hours, and only after much manipulation only one-half c.c. of serum could be expressed from four c.c. of blood. The patient was a Type III (Moss), and his serum undiluted or diluted one to two caused marked hemagglutination of cells of three donors of the same group, suspended in 1½ per cent sodium citrate in normal saline. Dilutions to one to four were sufficient to inhibit this phenomenon. The red cells of the patient showed no abnormal response when mixed with various sera.

The blood chemical studies are included in table 3. In addition, tests for Bence-Jones on the serum were doubtful. No precipitate resulted after heating for one hour at 56° C. At 60° C there was a minimal cloudiness, considerably heavier precipitate at 70° C than with normal sera controls, and at 78° complete solidification occurred.

Roentgen-rays, suggested after the blood and urine studies were made, showed widespread involvement of the skull, vertebrae, ribs, clavicles, pelvic bones, sternum, typical of multiple myeloma, and a few punched out areas of decreased density were seen in the femurs.

The diagnosis of multiple myeloma was made. The patient went progressively down hill, and left the hospital for his home after a week's stay. He became stuporous, bleeding from the gums continued, and death occurred in coma on February 18, 1934.

Consent for autopsy was not obtained until partial embalming had been done. The essential findings were as follows. The entire vertebral column, the ribs, clavicles, sternum, bones of the pelvis and skull showed numerous gray-white fleshy tumors varying from a few millimeters to several centimeters across, destroying the part of the bone involved. The last lumbar vertebra was nearly entirely replaced by tumor, and tumor had perforated the periosteum and extended into the soft tissues about the bone. Some of the vertebrae and ribs were so involved that they could be readily cut with a knife. Numerous tumor nodules and a diffuse gray growth were seen in the marrow of the femur occasionally eroding the cortex of the shaft. The kidneys were swollen, weighed together 340 grams, were soft and flabby, cut easily, and the sectioned surface bulged under the capsule. The parenchyma was pale and opaque. The capsules stripped readily leaving a smooth, gray, dull surface. The spleen weighed 240 grams and the pulp was moderately softer than normal and dull pink in color. The liver weighed 1800 grams, was pale, and the markings just visible. The other organs showed chiefly anemia, except the lungs, which were marked by hypostasis and edema. The thyroid and parathyroids were normal. The lymph nodes were not enlarged.

Histological study of the bone tumors showed them to be made of solid masses of plasma cells with typical round eccentrically placed nuclei and a moderate amount of cytoplasm (figure 3B). Some showed typical "watch-face" distribution of chromatin, but others much more hyperchromic nuclei, and many showed mitoses. Smaller foci of similar cells were present throughout many marrow sections. Many plasma cells of the same types were found in the spleen, a moderate growth was also seen in the lymph nodes, and a rather pronounced proliferation of similar cells was

found in the liver, both in the interstitial tissue about the periportal channels as well as in the sinusoids of the lobules. A few were found in capillaries in various organs. The kidneys showed changes similar to those in Case 3 below and also a few foci of plasma cell proliferation, and there was a diffuse edema of the stroma. Only a few casts were found in the collecting tubules. The convoluted tubules showed flattening of the cells and moderate granular degeneration. Vascular changes were slight. The glomeruli showed neither endothelial proliferation nor thickening of the basement membranes. The capillary loops were filled with a thick protein precipitate and only occasionally was a loop seen containing blood cells. In a few the afferent arterioles were engorged with blood, but the loops contained only protein, giving the appearance of obstruction of the loops by the protein.

The final summary was: widespread multiple myeloma, renal insufficiency due to glomerular obstruction, plasma cell growth in liver, spleen, lymph nodes, and kidneys, severe anemia, hypostatic hyperemia and edema of lungs.

CASE III

J. M., male, 52 years of age, was admitted to the Pasadena Hospital under the care of Dr. J. B. Luckie with the following history. He had suffered an acute illness in January 1931 which was diagnosed influenza by another physician. He had never quite recovered his strength and capacity for hard work following this, and had been going to his physician chiefly because of loss of strength and energy until October 1931, when he was told that he had anemia and that he would do better if his teeth were extracted. Eleven teeth were extracted and bleeding began immediately and continued in spite of the fact that his dentist gave him horse serum subcutaneously. He continued to bleed for about three weeks, when he was first seen by Dr. Luckie, who treated the gums locally and injected thromboplastin without any effect on the bleeding. He was admitted to the Pasadena Hospital November 9 and died eight days later. On examination he appeared very weak, markedly anemic, there was some bleeding from the nose, much bleeding from the gums, and crusts of blood were present on the lips and about the gums. The heart was not enlarged, and the lungs and abdomen were not remarkable. There was no evidence of purpura in any part of the skin. The lymph nodes were not enlarged. The temperature was normal, the pulse 108, and the blood pressure 165/110. There was no edema at any time.

During his stay at the hospital he continued to ooze from the gums in spite of intravenous calcium and one transfusion on November 12 of 500 c.c. of blood. During the last few days of life he was in a marked coma, Cheyne-Stokes breathing occurred on November 16, and he died on the seventeenth.

Six urinalyses showed a specific gravity of 1.011 to 1.017. There was always one to two plus protein, as demonstrated by Exton's sulphosalicylic reagent. This was not heated to boiling, and Bence-Jones protein was not sought for. In all specimens there were many hyaline, coarsely and finely granular casts, and a few renal epithelial cells. Only rarely were red cells and occasional leukocytes found. The blood findings are included in table 2. Clumping of the red cells in masses mixed with protein occurred in pipettes, using Hayem's solution as a diluent. Citrated saline was satisfactorily used. Examination of the smear showed a moderate achromia of the red cells and as in the preceding cases, a marked rouleau formation, even in the thin parts of the film (figure 1C). Only slight evidence of regeneration was seen. The polymorphonuclear neutrophils showed a marked shift to the left, and some toxic budding was seen. No immature granulocytes were found. There was profound acceleration of the sedimentation rate, and bleeding from puncture of the ear was as marked at the end of 20 minutes as at the start, and was controlled by pressure. Marked prolonged clotting time and prothrombin time were found. Addition of three drops of 5 per cent calcium chloride to uncoagulated plasma failed

to accelerate clotting. The serum of this patient caused marked rouleau formation with cells of donors in the same blood group (Group IV Moss). The blood chemistry findings are given in table 3. It is regretted that the blood proteins other than the fibrin were not studied. The clinical diagnosis was always in doubt and multiple myeloma was not suspected. He was considered to be a case of atypical chronic nephritis.

An autopsy was done the day following death and the body had been embalmed by arterial injection. Briefly, the major points of interest were as follows. Throughout the vertebrae, ribs, sternum, and shaft of the right femur the marrow was markedly hyperplastic, red-gray in color, and in the femur could be removed in chunks without breaking. There was only slight absorption of the bony trabeculae in the vertebrae, ribs and sternum and no distinct tumor or enlargement of any of these bones could be seen. Grossly the appearance resembled markedly that of a leukemic process.

The kidneys weighed together 380 grams, were markedly swollen, cut easily, and felt soft. The cortex was about 9 mm thick. It was gray, opaque, and the striations were just visible. The capsules stripped readily leaving a perfectly smooth surface. The spleen was normal in appearance, and the liver not remarkable. There was no enlargement of the lymph nodes. A slight bronchiectasis was found in the left lower lobe. The heart was moderately hypertrophic and weighed 450 grams. The valves were normal. There was minimal sclerosis in the coronaries and other arteries. There were no noteworthy changes in the thyroid or parathyroids.

Histologic examination of the bone marrow in smears and sections showed a nearly complete replacement of normal bone marrow by a diffuse growth of plasma cells showing typical eccentric, spheroid nuclei with an abundant cytoplasm, in many of the plasma cells vacuolization and granular degenerative changes were found (figure 3C). Most of the cells showed a typical "watch-face" distribution of chromatin and only a few showed immature nuclei. There was practically no absorption of the bone trabeculae in the sections made of the vertebrae, the growth appearing to grow diffusely through the marrow. There were no infiltrations in the spleen, liver, kidneys, or lymph nodes. The kidneys, a description of which is included as Case 86 in Bell's article,³⁰ showed as the principal finding a marked precipitation of protein in the glomerular capillaries, all of which were distended. The basement membranes of the capillary loops were not thickened, there was no endothelial proliferation, and in only a few of the loops were some red cells found and these failed to show evidence of clumping. The body had been embalmed and the red cells were apparently diluted by the washing-out fluid used, or possibly, as Bell suggests, the capillaries were obstructed by the concentrated plasma, which would naturally be more concentrated in the glomerular capillaries, where filtration of water takes place. There were only occasional casts found in the tubules and diffuse interstitial edema was present through the entire cortex, most of the convoluted tubules showed flattening of the epithelium, but minimal degenerative changes were present (figure 4). The rest of the organs presented nothing of interest except the lungs, which showed a profound edema and hyperemia of the alveolar walls. The protein precipitate in the lumina of the alveoli was very dense, much more so than that seen in a case with normal blood protein. Clumping of erythrocytes was not demonstrated in any of the organs, but this also may have been due to the dilution in the process of embalming. The final diagnosis was diffuse myelomatosis with renal insufficiency, due to blocking of the glomerular capillaries.

CASE IV

M. C., Italian housewife, age 55, entered the Buffalo City Hospital September 19, 1928. The history was obtained through an interpreter. She complained of an

increasing weakness, loss of appetite and anemia for the past nine months. She had had occasional dizzy spells during this period and occasional headache. There had been no vomiting, or pain in any part of the body, and inquiry as to symptoms referable to the various systems was negative except for those above mentioned.

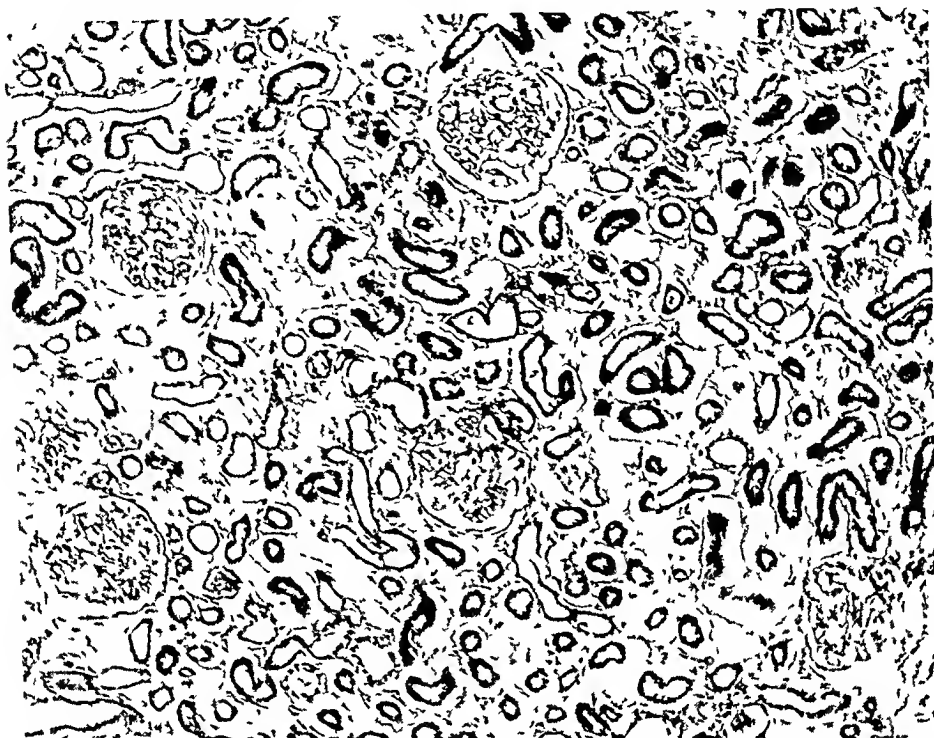


FIG 4 Case 3 Kidney section showing edema of stroma, dilated tubules and glomerular capillaries dilated

On examination she showed marked pallor and evidence of considerable loss of weight. There was no edema. Examination of the heart, lungs, abdomen and extremities was essentially negative, as was also the vaginal examination. No cause for bleeding was found. Two gastrointestinal series failed to reveal any evidence of disease. She was given several small transfusions but she failed to respond to these and finally left the hospital eight weeks after admission. Treatment of any kind was given with great difficulty because of her inability to speak English. Death occurred at home a few months later. No autopsy was permitted.

Laboratory examinations while this patient was in the hospital were as follows. The urine examinations showed a specific gravity of 1.012 to 1.014, occasionally 1.016 to 1.018, and no sugar. There was always a two to three plus protein, as demonstrated by Exton's sulphosalicylic reagent. Multiple myeloma was not suspected and no tests for Bence-Jones protein were made. The sediment showed occasional finely and coarsely granular casts and some waxy and hyaline casts. Phenolsulphonphthalein excretion in two hours was 35 per cent. The blood pressure was 125/70, the blood Wassermann test was negative, and the basal metabolic rate was plus 11 per cent. The hematologic findings are included in table 2. The red cell counts were all made with citrated saline as a diluent, since marked precipitation occurred when Hayem's solution was used. The smears showed marked rouleau formation (figure 1D) even in the thin portions, the cells averaged considerably smaller than normal in

size and showed a moderate achromia. There was very little evidence of regeneration. The polymorphonuclears at all times showed a moderate shift to the left with some toxic budding. The blood chemistry findings are included in table 3. There was no coagulation of the serum in heating at 56° C for half an hour. The significance of the rouleau formation and the hyperproteinemia were not appreciated at the time, and the patient was discharged with a diagnosis of atypical chronic nephritis with secondary anemia.

The first clue to the diagnosis in the first two cases was presented by examination of the blood smear, which showed a most marked rouleau formation in even the thin parts of the film, although they were made promptly and dried quickly. The diagnosis was made presumptively in the second case before learning anything about the patient except that he had severe anemia and spontaneous bleeding without fever. Suggested chemical studies and roentgen-ray studies corroborated the first impression. The same rouleau formation in smears and the clumping of the red cells in Hayem's solution in the red cell pipette was noted in the third case but not understood at the time, and the diagnosis was not made until the autopsy. Likewise the fourth case was not recognized immediately in spite of the same phenomena in the red cells and the marked hyperproteinemia, the significance of which was not appreciated at the time. However, the tentative diagnosis can reasonably be made after reading Reimann's article and after considering the other cases in the above series. The four cases demonstrate that hyperproteinemia particularly occurs in those cases excreting slight amounts or no Bence-Jones protein. The finding of most widespread involvement of the bone marrow as in the three proved cases corresponds to the descriptions of other cases showing increased blood proteins.

The last two cases, which were diagnosed chronic nephritis, support the clinical observation of Bannick and Greene that multiple myeloma should always be considered in atypical cases of renal disease. Renal insufficiency was seen in the last three cases. In the two cases which came to autopsy it was unattended by any of the usual pathological findings in the common kidney lesions found in azotemia, or by the plugging of the tubules by casts as reported in those cases excreting much Bence-Jones protein. Precipitation of thick protein, as described by Bell in Case 3 was observed in the glomeruli in both of these cases (2 and 3). However, the possibility of a functional plugging of the glomerular capillaries also by the clumps caused by intravascular hemagglutination must be considered. In Case 1 this phenomenon was plainly seen in the retinal veins when the circulation was slowed by firm pressure on the eyeball. The slowing up of the blood stream in the capillaries, plus the increased viscosity of the plasma due to glomerular filtration, might well favor a similar clumping in the glomeruli, as was seen in the eye of the only case of the series studied with the ophthalmoscope. Fahraeus reports that he believes rouleau formation occurs in the streaming blood, and that it can be demonstrated in cases showing a high sedimentation rate due to increased globulin or fibrinogen, by microscopy of the capillaries of the

nail bed or in the retinal vessels by the ophthalmoscope. He further states that intravascular aggregation of the red cells may be of even greater pathological importance in diseases than has been thought. He has shown by experiments with narrow glass capillary tubes, that a considerably greater pressure is necessary to force blood showing pronounced aggregations of erythrocytes through the tubes than normal blood.

The case of Wintrobe and Buell also presented symptoms which might well be explained on the basis of capillary obstruction. A peculiar mottling of the arms and lower limbs, blueness of the fingers, tips of the nose and the ears, and later coldness and blanching of the hands, feet and even of the tongue occurred and finally bilateral thrombosis of the retinal vessels. For want of a better term the condition was diagnosed Raynaud's disease.

It is regretted that autopsy was not performed in Cases 2 and 3 before embalming, with the subsequent dilution of the blood by the fluid, thereby destroying histological evidence of intravascular hemagglutination, but it is hoped that cases in the future will be studied with this in mind.

Possibly changes in the osmotic pressure in the glomerular vessels may explain in part the retention of nitrogen, since the tendency for the blood with an increased oncotic pressure due to increased proteins is to hold electrolytes and absorb water from the tissues. Peters and Van Slyke³¹ state that as the blood advances in its course to the capillaries (glomerular in the cases under discussion), the oncotic pressure increases due to concentration that has resulted from loss of blood water at the arterial end of the capillary, until it exceeds the hydrostatic (blood) pressure, and at the venous end of the capillary the flow of fluid is reversed, passing from the tissues into the blood. If the oncotic pressure in hyperproteinemia cases is increased, and as usual the blood pressure is low, it would seem reasonable to assume that there would be a decreased water output in the glomeruli, and consequent to this a diminution of excretion of nitrogen bodies.

The marked increase of uric acid in all the cases is no doubt due to the marked increase of purines from breakdown of nuclei in the tumor growths. The calcium increase is apparently due to the profound destruction of the bones. The parathyroids appeared to be not responsible for this phenomenon.

The abnormal bleeding in Cases 2 and 3 with the marked prolongation of both clotting and bleeding time in the presence of abundant fibrinogen, only slightly reduced (Case 3) or normal platelets (Case 2), and abundance of calcium is very difficult to explain. I have been unable to find similar instances in the literature.

The plasma cell growth in the spleen, liver, lymph nodes and kidneys of Case 2 without evidence of plasma cell leukemic changes in the blood is unusual, but similar findings are reported by Barr,³² and several cases with much more bizarre pathological observations by Jackson, Parker and Betha,³³ who believe the disease should be classed as a malignant lymphoma.

SUMMARY

In four cases of multiple myeloma, profound autohemagglutination of the red cells occurred in dry and wet films, and difficulty in counting erythrocytes because of granule formation in the red counting pipette was encountered in two cases. Marked hyperproteinemia was proved to be present in three cases, was apparently present in the fourth, and seemed to be the cause of these abnormal phenomena. Renal insufficiency apparently resulted from plugging of the glomerular capillaries by inspissated protein and possibly by the clumping of erythrocytes or changes in osmotic pressure due to the increased protein. Intravascular clumping was demonstrated during life by the ophthalmoscopic examination of the retinal veins in one case when pressure sufficient to slow down the circulation was applied externally on the eyeball. Prolonged uncontrollable bleeding and clotting time and increased calcium content of the serum with little changes in platelet count occurred in two cases.

The findings of marked rouleau formation in the smears of two of the cases led to procedures finally making the diagnosis of multiple myeloma.

Multiple myeloma with resultant renal abnormalities should be suspected in cases of atypical nephritis.

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THE TUBERCULOSIS OF CHILDHOOD *

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TUBERCULOSIS in childhood has many clinical manifestations. It can assume many forms which are seen predominantly in children and in addition many others seen in adult life. Only in recent years has its importance been realized, since the difficulties in diagnosis, and the insidious and occult forms in which it occurs have made it easily overlooked. There are many prevalent misconceptions about the disease, and several misleading pseudo-descriptive terms are imbedded in the terminology. Many writers on the subject are students of adult tuberculosis, pathologists or radiologists. This paper presents the point of view of the pediatrician, in the light of an active hospital service and the thorough pathological studies of Dr. Waldemar Grethmann.

Many physicians think that all children are infected, and that so-called "tuberculous infection" means little and may be disregarded unless "tuberculous disease" supervenes. This is a most dangerous view and often leads to neglect of children who deserve care. Those who hold this view entirely miss the value of a positive skin reaction. As a matter of fact, there can be no infection without disease since infection with the tubercle bacillus means that it has lived and grown in the body of its host and has set up its characteristic pathological lesions. No matter how small, how deeply seated, how obscure such lesions may be, they always carry the threat of serious results from dissemination. As Krause has said, "No tubercle is innocuous" (Figure 1).

On the other hand many physicians do not realize that serious tuberculosis is not at all rare in infancy. Even in hospitals where every method of study is available the autopsy often surprises the clinician, and in private practice it is inevitable that the disease should be frequently overlooked. A health officer in a suburban county told me that not a single case of tuberculosis had been reported as a cause of death in over two years in his county. Yet the county sanatorium was full of adult cases. The diagnosis is not always easy, but is missed most often from failure to think of its possibility.

The terminology of the disease is full of confusion. Such a term as "childhood type of tuberculosis" is objectionable since it infers that children have only one form of the disease, i.e., the primary complex (primary focus plus regional lymph nodes). It is true that this stage is seen mostly in childhood, but is very often only a part of the story. Even very young children may show forms of the disease in various organs of the body, corresponding to those which we are accustomed to see mostly in adults. Moreover, the primary complex may occur later in life.

* Read at the Chicago meeting of the American College of Physicians, April 16, 1934.
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"Masked juvenile" tuberculosis is a term used to describe the deep-seated, least manifest forms seen in later childhood. It is "masked" merely by the difficulties of diagnosis and is not a real form of the disease. Another term for these forms is "occult tuberculosis" as proposed by Engel. Still other terms such as "active" and "latent" disease are used with vary-

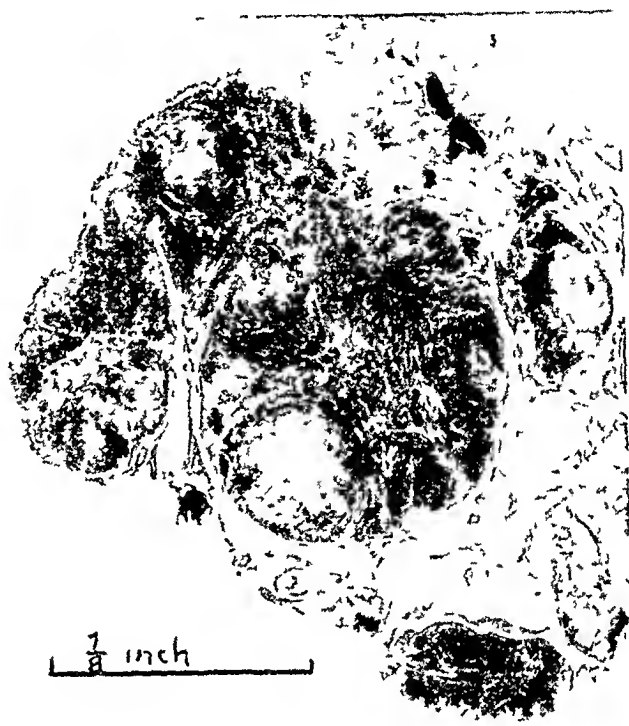


FIG 1 Section of small lymph nodes taken from the neck of a child who died of tuberculous meningitis. The larger central node actually measured only $1/8$ by $1/4$ inch yet in it there were caseating tubercles and in the smallest node next it, was still another. These nodes are so small as not to be palpable through the skin yet contain caseous material capable of being disseminated and of setting up fatal disease. Yet such a child, before the advent of meningitis, would be considered by some an instance of mere "tuberculous infection."

ing meanings by different authors. Certain pathological terms used with loose meaning, i.e., "hilus tuberculosis," "epituberculosis," "miliary tuberculosis" (often used for disseminated pulmonary lesions of bronchopneumonic type) have further confused the general understanding of the disease.

An important point of contention is the relation of adult tuberculosis to that acquired in childhood. One school holds that adult disease is a reinfection from without or exogenous infection, in an individual whose immunity reactions have been altered by preceding disease. The proponents of the theory of endogenous infection believe that adult disease results from a dissemination which has occurred from a tuberculous focus acquired during childhood. The evidence is conflicting and many facts may be interpreted for either view. It is possible that both may be right. Both sides

agree, however, that tuberculosis in adults is probably most often seen in those who have been infected in childhood. Therefore a clear conception of the sequence of events taking place in the infected child is of prime importance for the understanding of tuberculosis.

Too often tuberculosis is thought of merely as isolated disease in one organ, i. e., the lung, a bone or joint, the meninges and so forth. In textbooks on pediatrics, medicine and surgery descriptions of clinical forms are scattered from cover to cover, and in only a few is any orderly description attempted. But the disease really goes on in a definite sequence from initial infection to the end, in much the same way as syphilis or other infections, though no complete parallelism should be drawn.

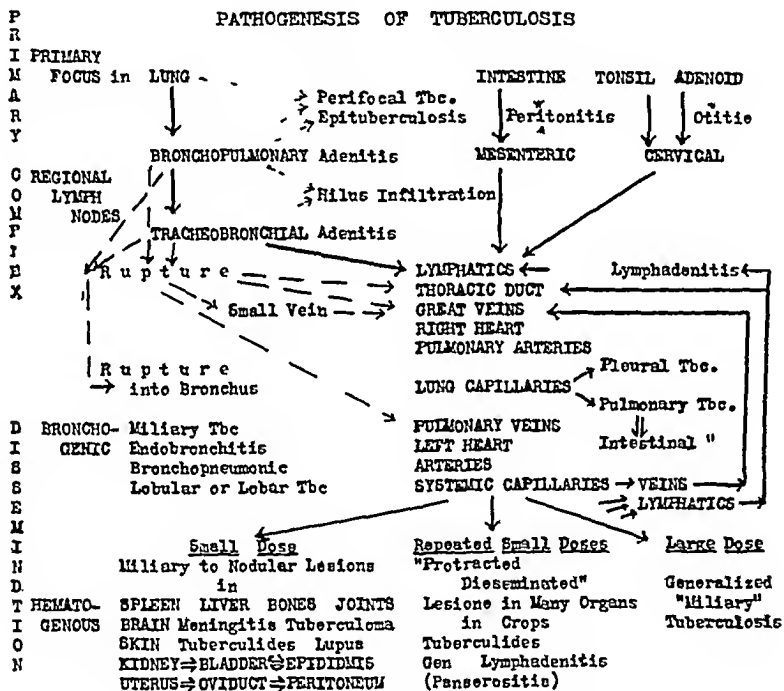


FIG 2 PATHOGENESIS OF TUBERCULOSIS. In the above the solid arrows indicate transmission of bacilli through lymphatics or blood vessels, broken arrows rupture into vessels or air passages. The dotted lines show direct extension to adjacent structures. Double arrows through intestine or genito-urinary passages. Some probable pathways have been omitted to avoid too great complexity. Thus perifocal or bronchogenic tuberculosis may also infect the intestine secondarily.

Tuberculosis in childhood has been under study on the Children's Medical Service of Bellevue Hospital for the past 18 years. The material is peculiarly suited to obtaining an understanding of all the forms of tuberculosis occurring in childhood. Many patients are sent in from other hospitals as soon as the diagnosis is made, others are admitted for acute illness and are discovered to have tuberculosis. The large out-patient service picks up the forms of early and ambulatory disease. This combination of acute

and not acute material should be more instructive than that obtained from the tuberculosis clinics or sanatoria. There has been a large follow-up class, at first as an offspring of the original Nutrition Class. For over 10 years Dr. Edith Lincoln and her associates have had direct charge of all chest cases, both in the hospital wards and the chest clinic of the out-patient department. Much has been added to our information by this long continued follow-up and by the pathological studies of Dr. Grethmann.

PATHOGENESIS

A clear conception of its pathogenesis is necessary for any interpretation of the disease. It is a well known fact that in all tuberculosis there must be a primary focus. The bacilli are ingested, inhaled, or find lodgment on any part of the physiological surface of the body. There they set up their characteristic early inflammatory lesion. In various autopsy series the primary focus has been discovered in 90 to 95 per cent of cases showing tuberculosis.

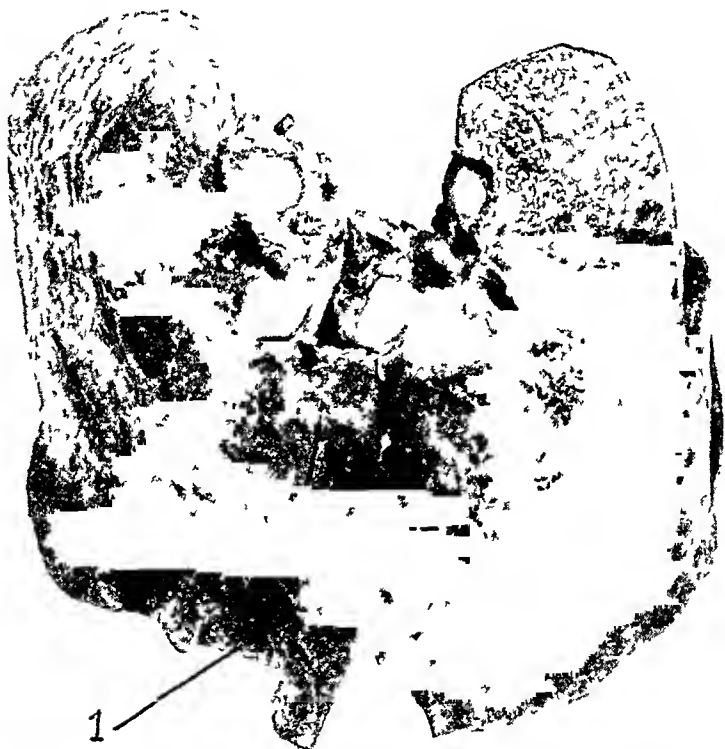


FIG 3 Primary complex in an infant. Primary focus shows as white spots (cut through at bottom of photograph (1)). Regional lymph nodes in hilus region. Note small size of primary focus with large lymphadenitis. (Prepared and photographed by W. Grethmann.)

The size of this, as of all tuberculous lesions, depends largely on the number of bacilli which initiate the process. The dosage of bacilli is thus an important factor. The primary focus is most often in the lung, usually in the

lower part of the upper or in the lower lobe, near the pleura. From the primary focus the bacilli are rapidly carried in the lymphatics to the regional lymph nodes, and there set up a tuberculous adenitis. The site of this, of course, depends on the site of the primary focus. In the lung the first nodes involved are the bronchopulmonary which lie in a chain along and close to the main bronchi. Bacilli passing through these are often filtered out in the tracheobronchial nodes about the bifurcation of the trachea and set up an

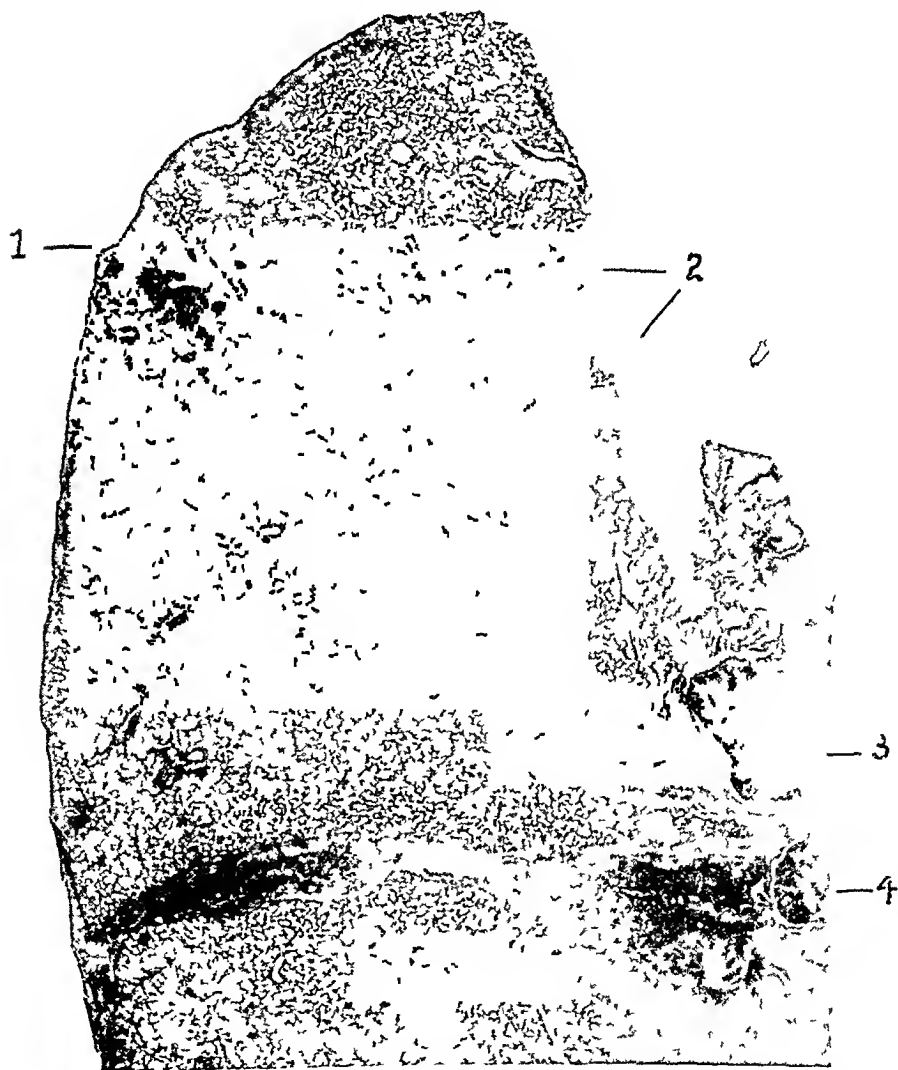


FIG 4 Primary complex. Section of the right upper lobe of an infant dying from acute bronchopneumonia of lower lobes. This section accidentally cut through a primary focus (1) composed of several tubercles just under the pleura. It shows a few tubercles along the septa (2) and tuberculosis of a bronchopulmonary node (3). Just below this is a normal node (4). No bronchopneumonia shows in this section. This is a very early primary complex.

adenitis here or in the chains of paratracheal lymph nodes. The close proximity of these chains of nodes to the air passages and veins in the lung and mediastinum is of vital importance (Figures 10 to 13)

The combination of primary focus and regional lymph nodes makes up what Ranke has named the primary complex. It exists in every individual who has been infected with the tubercle bacillus. This is what is commonly called "childhood type of tuberculosis"—a clumsy and misleading phrase for the reasons given above. The primary complex merely represents the pathology of all first infections. When it occurs in infants and young children there is apt to be a larger adenitis than in cases acquired in later childhood, perhaps because the infant is often exposed more intimately and to larger doses of bacilli if he is exposed at all (Figures 3 and 4)

The primary complex may occur elsewhere than in the lung, though less commonly. A primary lesion in the intestine with mesenteric nodes, perhaps extension to the peritoneum, is second in frequency. The tonsil or adenoid with cervical nodes is the third. Extension to the middle ear occurs in rare instances. Other primary lesions in skin and mucous membranes are rarer.

The roentgen-ray findings give us a means of studying pathology even during life. In the primary complex there are no shadows in the majority



FIG 5 Roentgen-ray showing definite enlargement of left hilus shadow due to tuberculous bronchopulmonary nodes in a small infant. No calcification. No trace of the primary focus is visible on the film although it was easily found at autopsy in the left upper lobe. The right hilus is within normal limits although larger and more mottled than the average normal. The mediastinal shadow is slightly widened.

of cases until calcification has begun. If the primary focus is larger than usual, one may occasionally see one or more small soft shadows in the outer

part of the pulmonary field but they are so inconspicuous as to be easily overlooked. In some cases where serial films are taken it is possible to recognize the site of the primary focus after calcification has taken place and then to pick out insignificant shadows in the earlier film in the same place. Early bronchopulmonary adenopathy may be seen as suspicious enlargements in the hilus region but can only be diagnosed with certainty when calcified or when very large. (Figures 5 and 6) Tracheobronchial nodes widen the supracardiac shadow when very large, but considerable involvement may take place and be concealed behind the sternum. Lateral and oblique views are occasionally helpful, mainly when there is calcification.



FIG 6 Early calcification of primary focus over fifth right rib and bronchopulmonary nodes in hilus shadow. A film of the same child taken a year before showed a widening of the mediastinal shadow above the heart but no calcification.

The further course of the tuberculosis depends on several factors

I The course of each local inflammatory process

II A Extension to adjacent structures

To other lymph nodes

To lung parenchyma

B Extension by rupture into an air passage, or bronchogenic dissemination

III Generalization or hematogenous dissemination

I The *course* of the inflammatory process may be stationary, retrogressive, or progressive. It must be remembered that tuberculous lesions, like all inflammatory processes, have the possibility of resolution and complete healing. Most individuals who acquire a primary complex overcome the infection and go for many years, or through life, with no subsequent symp-

toms The primary focus and adenitis become resolved or encapsulated and calcified or even ossified They then show as dense shadows on the roentgen-ray film for many years

A tuberculous lesion may remain stationary for a certain period, neither retrogressing nor progressing Such lesions may then go on in either direction It is difficult to say just when we have this condition Much so-called "latent tuberculosis" is found to be slowly progressive

The lesion may become progressive and go on to caseation, but even then heal by encapsulation, fibrosis and calcification Or softening and cavitation may take place with discharge of the contents into a viscus or through the skin, etc

II (A) *Extension to adjacent structures* may occur in any progressive lesion

1 Extension from the lymph nodes to others may result in a general involvement of all the mediastinal nodes This often gives enormous masses of tracheobronchial and paratracheal nodes Even these may resolve slowly On roentgen-ray they may be seen as a widening of the normal shadow above



FIG 7 Primary focus extending to adjacent lung 1 Primary focus 2 Direct extension from primary focus 3 Bronchopulmonary nodes (Prepared and photographed by W Grethmann)

the heart which is often mistaken for the thymus. These shadows are sometimes asymmetrical and at times have suggestive rounded outlines.

Pressure on a bronchus may occur, obstructing respiration in a lobe or whole lung. We have had cases of atelectasis resulting in chronic fibrosis with bronchiectasis caused by prolonged pressure of a tuberculous lymph node.

2 The primary focus occasionally increases in size, involves more and more lung tissue until real pulmonary tuberculosis results, giving a shadow on the roentgen-ray more or less like pneumonia. This has been called perifocal tuberculosis (Figure 7). This may resolve or go on to caseation and cavitation. In the latter case the caseous matter may discharge into a bronchus and be disseminated through the lung as described below.



FIG 8 Hilus infiltration. A true tuberculous infiltration (2) extending outward from a mass of caseous bronchopulmonary nodes (1). (Prepared and photographed by W. Grethmann.)

3 Extension from bronchopulmonary or tracheobronchial nodes may take place into the adjacent lung parenchyma. These are often wedge-shaped lesions with the apex outward and are often benign, going on slowly to complete resolution. They may be seen to appear and gradually disappear in serial films leaving nothing except the calcifications of the original nodes. This is true hilus infiltration by a tuberculous exudative process. Some of these go on to caseation, however, and run the course of a caseous pneumonia, with bronchogenic extension, or walling off, fibrosis and calcification (Figure 8).

4 Epituberculosis is a term used by Ehasberg and others to describe cases in which massive lung shadows resembling pneumonia are seen, mostly in the upper lobes which gradually disappear. The term was coined because it was believed that the shadows were not cast by true tuberculosis but by

simple inflammatory exudates around a tuberculous focus. The latter may be seen in many cases as a residual calcification after disappearance of the massive shadow. There are other possibilities explaining these shadows. They may be due to real tuberculous exudates which resolve in time, like those described above. Several of our autopsies on cases having shadows believed to be epituberculosis have shown definite tuberculous pneumonia. The third explanation is that there is pressure on a bronchus by an enlarged node, and behind it an atelectasis, or a lung filled with exudate analogous to the "drowned lung" described by Jackson in certain cases of foreign body in the bronchus. Bronchoscopy may reveal an obstructive pressure in some instances of epituberculosis. Whatever the exact pathology of this group, it is important to remember that massive shadows in the lung appearing after infection with tuberculosis do not always mean progressive caseous pneumonia, but at least a reasonable hope may be held out that complete recovery is quite possible. (Figure 9)



FIG 9 Epituberculosis? The large shadow in the right upper lobe was thought to be a lobar pneumonia at first. But it persisted for two months and then gradually cleared leaving a dense calcified focus in the center. By some this is called "the evolution of the primary focus," but it seems more likely that it is a perifocal reaction, either a simple exudative process or the result of bronchial compression and atelectasis. Since calcification takes one or two years it is probable that the focus now calcified has been present before the massive shadow develops. In other cases we have been able to watch this sequence.

(B) *Bronchogenic dissemination* takes place when a caseous node or tuberculous cavity ruptures into an air passage. This is not an uncommon accident on account of the close apposition of the nodes to the trachea and bronchi. It is always a serious matter. The resulting lesions in the lung depend largely on the amount of caseous material inspired. Caseous ma-

terial and bacilli scattered through the lungs in small amounts cause scattered lesions of miliary size, or bronchogenic miliary tuberculosis. Larger amounts cause an endobronchitis or bronchopneumonia. Still larger amounts may cause a lobular or even a lobar pneumonic lesion. The seriousness of all these lesions is increased because they are on an open surface, ulcerative and progressive. They usually go on to chronic cavernous phthisis as seen in adults (Figure 10).

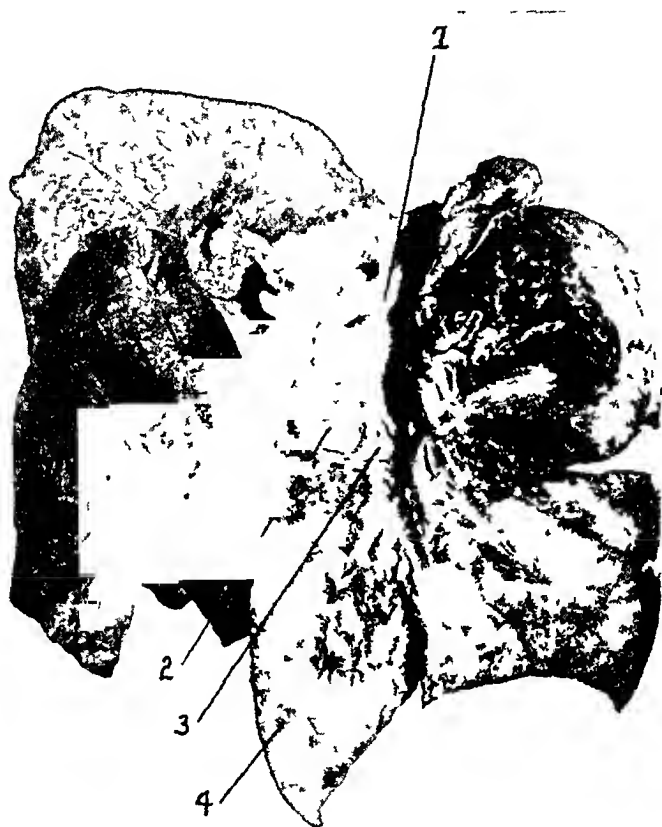


FIG 10 Bronchogenic dissemination with lobar caseous pneumonia. 1 Lumen of large bronchus. 2 Caseous bronchopulmonary node. 3 Rupture into bronchus. 4 Caseous pneumonia of lower half of lung. In this case the caseous node had ruptured into the bronchus with a resulting aspiration of a large number of bacilli, giving caseous pneumonia of lobar extent. (Prepared and photographed by W. Grethmann.)

A proper roentgen-ray technic differentiates these just as in adult cases. Many times a bronchogenic dissemination is diagnosed as "miliary tuberculosis" from the film. To the most casual observer the lesions are not only of various sizes, but most of them are much larger than miliary. Lobular pneumonic tuberculosis gives larger mottled shadows and lobar tuberculosis massive shadows like lobar pneumonia. (Figures 11, 12 and 13.)

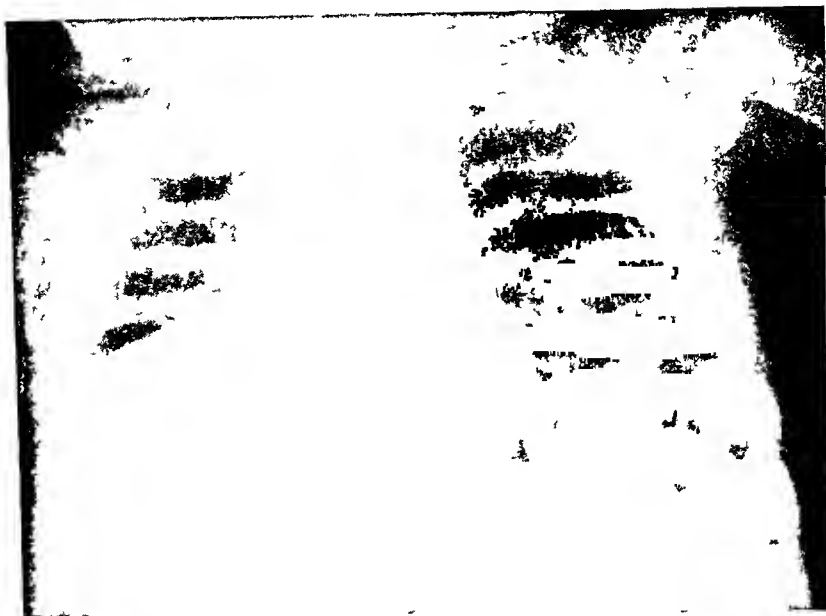


FIG 11 Roentgen-ray of chest of colored infant. Physical signs of consolidation in right lower lobe, thought to be pneumonia? Note that heart and mediastinum are pushed to right probably by compensatory use of left lung, and perhaps by beginning obstruction of right main bronchus. Mediastinal shadow is wide, even allowing for displacement.



FIG 12 Same patient as figure 11, two weeks later. Beginning cavitation in center of right lower lobe consolidation. Diffuse mottling of upper right and all of left pulmonary fields. This represents bronchogenic dissemination from discharge of cavity into air passages. Films of this kind are often read as "miliary tuberculosis." The shadows are too large and vary too much in size for this diagnosis.

Extension from bronchogenic tuberculosis may take place through the trachea and larynx to the gastrointestinal tract. The larynx is rarely involved in childhood. But the bacilli which are coughed up and swallowed



FIG 13 Right lung of patient whose roentgen-rays are shown in figures 11 and 12. Lung is split from pleura to hilus and laid open. Note the caseous pneumonia of the lower lobe, probably from rupture of a lymph node into a bronchus. Cavitation in center. The upper lobe shows nodules of many sizes due to aspiration of the contents of the cavity. The left lung was like the right upper lobe. There was an enormous adenopathy of the tracheobronchial and paratracheal nodes. A fistula in ano showed tuberculosis and there was extensive involvement of the mesenteric nodes. There was tuberculosis in the liver, spleen and meninges, i.e., hematogenous dissemination.

may set up a tuberculous enteritis with mesenteric adenitis and a serious result. This is often missed entirely by the clinician, since diarrhea is not constant. Severe progressive emaciation is characteristic. Calcified abdominal lesions may sometimes be seen on the roentgen-ray film.

III *Hematogenous dissemination or generalization*. This may begin early even during the development of a primary complex. This may begin blood stream in several ways. In the first place the lymph nodes are never perfect filters and bacilli pass through them to the lymphatics, thoracic duct and great veins. Or by rupture of caseous nodes into the thoracic duct, or a great vein, the same result is obtained. Furthermore, the presence of a small hemorrhage in one of the large caseous nodes often points out the site of a rupture into a smaller vein. Rupture into a pulmonary vein discharges bacilli directly into the greater circulation.

Bacilli reaching the veins of the systemic circulation are carried through the right heart and pulmonary arteries to the lung capillaries. They may find lodgment and set up lesions in the lung or in the pleura. This is one of the possible sources of pulmonary tuberculosis.

But the lungs are also imperfect filters and bacilli pass through them to the left heart and the larger circulation. They are then carried to various organs of the body where they may set up new lesions. The resulting lesions found depend on the doses of bacilli injected into the circulation, the lapse of time since the dissemination, and how often such dissemination has occurred. Three forms of hematogenous tuberculosis may be recognized.

1 A single small dose may lodge in any one organ or in several, and there set up lesions whose local course may be benign or serious, depending largely on the importance of the organ involved, and the further course of the process. Thus in brain, meninges, eye or kidney the result is usually serious, while in bone, liver and spleen it may be much less so.

The lung involvement may show in the roentgen-ray as soft shadows of miliary or small nodular size. They are often found at the apices or in the upper part of the lungs. They may calcify later. In adolescent children they are called "Simon foci" since Simon first described them. There is still discussion as to whether these lesions may be the method of development of adult apical tuberculosis.

2 A single large dose gives a generalized tuberculosis with lesions of equal size all over the body, often called "general miliary tuberculosis." But "miliary" again refers to the size of the lesions and this generalized form often has lesions of nodular size if many bacilli lodge in one site. The roentgen-ray films of the lung show many small soft shadows of about the same size and in varying numbers. They may be few and, at first, so small as to be invisible, but become apparent as they enlarge with time. It is possible for these lesions to be present in the lung for a long time since the tubercles are not on the surface as in bronchogenic dissemination and so are less apt to ulcerate. They may even heal.

3 Repeated doses of varying amounts give lesions of different sizes and different ages. They are found in various organs, the lungs, the kidneys, the liver and especially the spleen, where they appear as the so-called "large nodular spleen tuberculosis." Besides these various parenchymatous lesions there is usually present a tuberculous lymphangitis and lymphadenitis of groups of lymph nodes in various parts of the body. In this form of hematogenous tuberculosis we may also find an extensive involvement of the various serosal surfaces. With each dose of dissemination a crop of tuberculides may appear in the skin. The pathological picture of this form of hematogenous tuberculosis was first pointed out by Schuermann of Hamburg, who coined the term "protrahierte Durchseuchung." This may be best, but not quite accurately, translated as protracted dissemination. Dr. Grethmann deserves credit for having elaborated as a clinical entity this form of hematogenous tuberculosis which is not uncommon but which ap-

parently is not generally known. He has collected a series of about 70 cases of this form in individuals of different ages, which will be published in the near future. After seeing some of his autopsies we have been able to determine this form of tuberculosis in a number of children, from the repeated new lesions, crops of skin tuberculides, varying sized shadows in the lungs, calcified nodules in the spleen, general adenopathy and sometimes panserositis.

In involvement of the genito-urinary tract transmission is usually from the kidney to the bladder and thence to epididymis. But a lesion in the latter may appear first and extend to the bladder and prostate also.

It must be repeated that the further course of any lesion set up by any of these means of dissemination may be progressive or stationary or retrogressive. The character of these secondary lesions is altered by the change in the body reactions due to the previous injection into the system from the primary infection of the products of the growth of the tubercle bacilli and by the resistance of the host.

From the foregoing, which is based on numerous cases under each pathological entity described it is obvious that tuberculosis is found in children in many forms besides the usual one supposed to be characteristic—"the childhood type." A failure to keep in mind the inevitable sequence of events leads to all sorts of illogical classifications in which the primary focus and then the lung lesions are described in detail, and later the tracheo-bronchial adenitis. Such a divorce of the two elements of the primary complex is unnatural and confusing. In some books general military tuberculosis is described first among the clinical forms.

INCIDENCE

The incidence of tuberculosis in childhood depends largely on the amount of exposure to open adult cases—that is to the amount of adult disease active in the community. Hence it is more common in cities, in the crowded slums, and more in European cities than in this country. It is much less prevalent in the better classes of society, in smaller towns and in most rural populations. Exposure to an open case in the family or to a servant is the usual source of infection. The disease in this country, is nearly always of the human type.

There are two measures of the incidence namely the tuberculin skin reaction and the death rate. There is a widespread impression among physicians that the tuberculin reaction is of little significance, and that practically all children after infancy are infected and give a positive reaction. This is far from the truth. The tuberculin reaction gives us very definite information as to whether a given child has been infected or not. A positive skin test shows that the tubercle bacillus has lived and grown in the child's body and has given off the substance we know as tuberculin, exerting a sensitivity of the body cells to further contact with tuberculin. It must be remembered that a positive tuberculin skin test does not tell whether the

disease is active or not, nor whether the lesion in which we are interested is tuberculous, but merely that the individual has been infected at some past time

Of the skin tests, the Mantoux or intracutaneous test has supplanted all others, since it is much more reliable than the Pirquet, Moro, or Calmette tests. It is generally used today in all pediatric services. The initial dose is usually $1/20$ to $1/10$ milligram ($1/20$ to $1/10$ c c of 1:1000 dilution) except in cases where massive or very active disease is suspected, where $1/100$ mg is safer. If the first test is negative it should be repeated with increasing dosage in all doubtful cases, using $1/5$, $1/2$ or even 1 mg. A different area should be used for each test since it is possible to sensitize local areas of the skin by reinjection. When a test has been definitely positive it should not be repeated for several months since the second reaction may be severe, especially if done on the same arm. The main sources of error are the use of inert or contaminated solutions, improper technic of injection, the presence of fever from intercurrent disease, or lowering of skin sensitivity by overwhelming tuberculosis. In the latter instance it may take 2 to 10 mg to excite a reaction, and since these patients are often moribund, they may die before the dosage can be increased sufficiently to give a positive test.

Care should be taken not to excite a generalized febrile reaction by too large an initial dose. This should never exceed $1/10$ mg. The local reaction is occasionally severe, even vesicular and occasionally necrotic, but this is rare and with proper forethought in giving small initial doses, should not discourage the use of the test.

Many series have been published showing the incidence of positive reactions in various parts of the world. Unfortunately the early series from Vienna and other European cities showed a very high incidence, up to 50 per cent at 7 and 95 per cent at 12 years. These figures were accepted as representing the prevalence of tuberculous infection everywhere. It is certain that they are much too high for the cities of this country, even in the population of the slums. Figure 14 shows the incidence curves in various series. The Bellevue statistics (the New York curve) have been recently compared with series from other hospitals in New York by Grolet and the curves are almost identical. They correspond closely to statistics from Minneapolis, Ontario, San Francisco and other parts of this country. In these series about 10 per cent of living children give positive reactions in the first two years, 15 per cent in the third and fourth years, 20 per cent at five to seven, 30 per cent at seven to nine, and only about 40 per cent at ten to twelve. Since all children are not infected the skin test becomes most important.

The death rate from tuberculosis is another measure of incidence. The death rate is high in the first two years, as high as any year until early adult life. It falls off rapidly up to five and the lowest rate is from five to 15, after which there is a steady rise. In other words tuberculosis is often a

fatal disease in infants, but relatively not fatal in school children. Moreover the death rate in infancy is undoubtedly much higher than statistics indicate, since many fatal cases are overlooked if no autopsy is performed. The diagnosis is obscure in infants and many deaths are attributed to marasmus or bronchopneumonia which are in fact due to tuberculosis. Yet

Mantoux Statistics

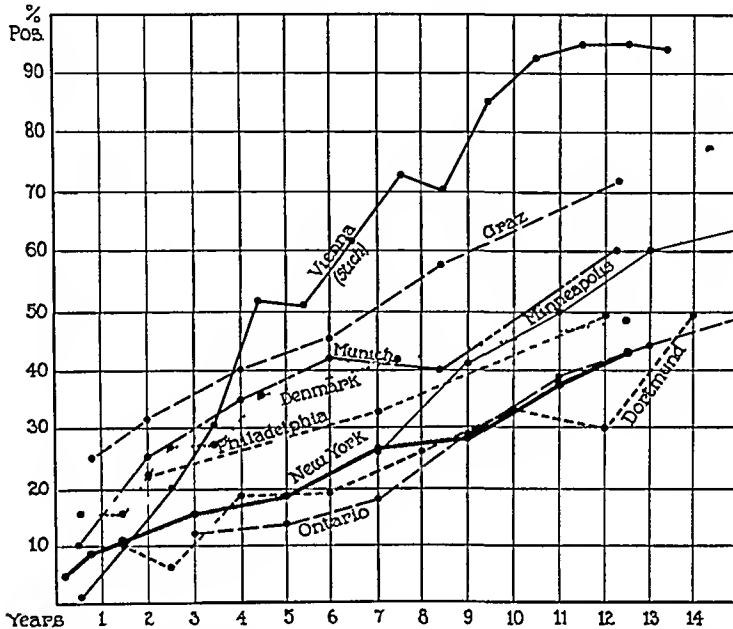


FIG 14. Curves showing incidence of positive tuberculin reactions in different parts of the world. Note that in nearly all cities the incidence does not exceed 50 per cent at 12 to 14 years. (Reprinted from "Tuberculin Skin Reactions" by Charles Hendee Smith, *Am Jr Dis Child*, 1929, *xxviii*, 1137.)

tuberculosis is not always fatal in infancy. It must be noted that while about 10 per cent of infants give a positive skin reaction, the total death rate is never as high as 10 per cent of the infant or child population at any age from tuberculosis, or indeed, from all causes. Therefore many must recover. Children infected after the first two years have a relatively good chance of handling the disease unless meningitis occurs.

The question is often asked as to whether it is better for the individual to be infected early or not. It is believed by some that an early infection gives a certain immunity to later serious disease. This may be true, since it has been found that nurses going into a sanatorium are less likely to acquire active tuberculosis if they have a positive skin test. On the other hand the child who is infected early is much more likely to have massive or progressive disease with fatal dissemination or meningitis than is the one infected somewhat later. It is certainly undesirable to have young children

infected. Therefore they should be kept from contact with open cases of tuberculosis.

The Calmette (B C G) inoculation with living attenuated bacilli is done with the idea of giving the infant a relative immunity during the years when he is most susceptible. The intracutaneous method is the best, the oral administration unreliable. The tuberculin reaction becomes positive, but after some years is said to become negative again. Since this seldom occurs in tuberculosis acquired in the ordinary way, it brings out the thought that the latter is rarely completely cured. The B C G inoculation is still under trial. Many feel that it is unjustifiable and dangerous, and time alone will tell whether the death rate is influenced sufficiently to justify its wide use among infants living with open cases. Some of the early reports have been hopeful.

CLINICAL VARIETIES

The clinical aspects of tuberculosis are different in infants (up to two or three) and in older children, and they need separate consideration.

Tuberculosis in Infancy

In infancy the primary focus gives few symptoms, no physical signs and no roentgen-ray shadow until it becomes calcified. A transient unexplained fever and perhaps failure to gain well are its only symptoms. The lymphadenitis gives no signs at first nor until the nodes are quite large. No suspicion of the disease may be aroused until enormous adenopathy, or bronchogenic or hematogenous dissemination has occurred, or until there is some serious or fatal complication such as meningitis. In fact the element of surprise is the predominant note in nearly all infantile tuberculosis.

The most common symptom complexes are the following:

1. Tracheobronchial adenopathy of large extent. Such infants usually have fever and do not gain well. The chest shows practically no signs, though occasionally parasternal dullness or an increase in the area of tracheal breath sounds may be noted. The roentgen-ray gives a wide supracardiac shadow, often rounded outlines on one side or both, suggesting nodes. Such shadows are often diagnosed as enlarged thymus. In the older infants the primary focus is occasionally calcified and there may be beginning calcification in the hilus region (bronchopulmonary nodes). There may be pressure obstruction of a bronchus with absent breath sounds over a lobe or a whole lung. With rest and care some children, even with masses large enough to cause obstruction, improve greatly and go on to slow recovery. The greatest danger is from rupture into a bronchus. (Figure 17.)

2. Cases of "marasmus." Small infants are admitted to the hospital with marked emaciation with or without irregular fever. There may have been a story of feeding difficulty, but many infants have done well at first and then have begun to fail. Routine roentgen-ray should be done on all such patients and may reveal definite tuberculosis in the lymph nodes or wide

dissemination, or even large cavities. This group usually has a bad prognosis.

3 Cases simulating pneumonia. Infants are admitted with relatively short histories,—fever, prostration, cough and physical signs of consolidation or with crackling, resonant rales at the bases suggesting bronchopneumonia. These infants may be emaciated but are often fairly well nourished. The roentgen-ray shows mottled shadows over part or all of the pulmonic fields, indicating bronchiogenic disseminated tuberculosis or localized consolidation much like a lobar pneumonia. In the latter instance only the long course, or beginning cavitation, or the finding of bacilli in the sputum makes the diagnosis. It is exceptional to have recovery in this type, although it may be impossible at first to differentiate a given case from those described as epituberculous. (Figures 11, 12 and 13.)

4 Unexplained high fever, without local signs, often turns out to be disseminated pulmonary or generalized tuberculosis.

5 A final group includes the cases which are definitely suspected of tuberculosis from the outset.

Tuberculous meningitis stands first in this group in frequency and seriousness. This is seen as a terminal event in widespread tuberculosis or it may be the first clinical manifestation. An infant who has been in apparently perfect condition suddenly becomes ill, with vomiting and fever, and irritability. Nervous symptoms soon appear, somnolence and coma, paralyses and so forth. Infants often lack the irritative signs seen in older children, such as stiff neck, positive Kernig and Brudzinsky signs, and are entirely flaccid with absent reflexes. There is a rising leukocyte count. The spinal fluid shows high protein, low sugar, mononuclear cells and bacilli.

Bone disease in infants is more common in the small bones of the hands and feet than in the larger bones. Dactylitis is often apparently destructive but may heal with rest and minimal surgical treatment leaving an almost normal bone. (Figure 15.)

Disease in other organs in infants is difficult to diagnose clinically. Liver and spleen tuberculosis give no symptoms, though the organs may be definitely enlarged. Kidney tuberculosis is seen much less often than in older children.

In the protracted disseminated form various organs may be affected. Thus a child of 18 months admitted to Bellevue with fever and a fresh crop of tubercles was found to have one radius, the opposite ulna and four metacarpal bones affected, as well as a massive shadow in one lung. Yet his nutritional state was not bad. Repeated crops of new lesions may occur in the skin and other organs. One case showed calcification of nodules of different sizes in the spleen on roentgen-ray. The prognosis is not altogether unfavorable depending somewhat on the number and size of the crops of new lesions, and the site of the main involvement, but it is in general

unfavorable This form will be discussed more fully in forthcoming papers by Lincoln and Grethmann from this service

Physical examination of the lungs is often most unsatisfactory in small children The stethoscope is the least useful instrument at our disposal in



FIG 15 Dactylitis of the bones of the hands of an infant with generalized tuberculosis

the tuberculosis seen in childhood The roentgen-ray may reveal large lesions in cases where no signs whatever can be elicited either before or after seeing the film Even massive consolidation or large cavities may be completely missed by the most careful examiner Inconstant râles, more or less resonant (crackling) are often the only signs heard At times definite signs of consolidation are made out in pneumonic tuberculosis or in "epituberculosis" Hilus infiltration even of large extent, is usually silent since it is surrounded by normal lung The need for the lightest percussion must be emphasized in examining all infants

Blood In all the acute and exudative forms of tuberculosis there is a leukocytosis It is often incorrectly believed that this disease gives a leukopenia, and an attempt is made to exclude tuberculosis when an increased leukocyte count is found Even tuberculous meningitis has a slowly rising leukocyte count The monocytes are increased in all active tuberculosis, but the difficulty of the technic makes the monocyte count a research rather than a clinical method

Tuberculosis in Older Children

If all older children who have been infected, as shown by a positive skin test, are thoroughly studied it will be found that they fall into the following groups

1 Recent infections in those who have been infected within two years or less, that is those who have a fresh primary complex. These comprise approximately 15 to 20 per cent of the reactors, as determined by the slope of the curve of positive tests. If calcification requires one and a half to two years the children infected less than that time show little on roentgen-ray, unless there is large adenopathy and this is less common than in infants. Some of these children may have a primary complex so insignificant as to give no symptoms, others may show real symptoms of activity during the acute stage.

2 A certain number will show calcification in the hilus region of the lung, perhaps a calcified primary focus in the parenchyma. But this group is not as large as would be expected. Binaid, Amberson and Loew found only 20 per cent of positive roentgenograms in a group of 1000 of high school age, reacting to tuberculin. We should expect the percentage to be less in younger children. Certainly many cases are seen in which no calcification nor signs of previous lung involvement remain. Of the children with calcifications some may have healed all their lesions, but others may still have active tuberculosis. The presence of calcification on a film does not mean complete healing.

3 Children who have been infected more than two years who have healed their lesions by resolution and show no calcification. They should be symptom free if healed. It is probable that some of the cases having symptoms of activity have lesions not demonstrable by our present methods.

4 A few have definite pulmonary tuberculosis. This is not a large group and does not tend to increase in size with age, because pulmonary tuberculosis in children is a serious and fatal disease, much less likely to become arrested than in adults. The older the child, the more does the disease approach that seen in adults.

5 A few have non-pulmonary tuberculosis in mesenteric nodes, cervical nodes, bones, kidneys or skin, etc.

The matter of importance is to try to make out whether the disease is active or not, since this is the keynote of treatment. Constitutional symptoms are more significant than roentgen-ray findings or physical signs. The child is too often forgotten in the study of his roentgen-ray shadows.

Nearly all the studies of tuberculosis in childhood have been based on roentgen-ray films. But if only 20 per cent of those infected are roentgenologically positive, and if many of these may have active lesions, the roentgen-ray as a diagnostic screen is not valid in picking out active cases. This has been shown again and again in surveys in which a large number of children have been roentgen-rayed and the positive cases then tested with tuberculin. This is not only a most extravagant method of selection, but a

most inaccurate one. The better way is to test the children first, then roentgen-ray the positive reactors *and in addition seek for signs of activity in all, regardless of the roentgen-ray findings*

The clinical picture of activity is characteristic and quite obvious to a trained observer. The symptoms and signs are few but added together should be enough to arouse suspicion of what is happening to the child.

Fever is an almost constant sign of activity—that is, a rectal temperature which rises above 100° nearly every day. Temperatures under 100° may be disregarded in childhood. The fever is irregular, rising to a different level on different days, and not always at its height in the afternoon. The highest point may be at any time of day or even in the middle of the night. The great irregularity is characteristic.

Failure to gain weight at the proper rate, and as a result more or less malnutrition, is always a suspicious sign. No other disease seems to exercise so prompt an effect on the nutrition in childhood. Gain in weight may occur in adults with advancing lesions, but is rarely seen in children. There is often secondary anemia.



FIG 16 Aspect of child of two years with active tuberculosis as shown by fever. Note the miserable, anxious expression. This child never smiled.

Languor, easy fatiguability, anorexia and irritability are all probably more or less due to the fever. These children act and look languid, unin-

terested in life. Some of the younger ones have a facies which is peculiar and suggestive of serious disease. The eyes look large, dreamy, or absent-minded, often lustrous. The child does not smile, nor can he be made to do so by any of the usual tricks of doctors or nurses. The lips appear to be thickened or pouting. This is perhaps a disuse phenomenon, since smiling is a regularly recurring matter in normal children. Such children may remain in this condition for months with complete apathy, never smiling once. Many have a fretful expression or one of anxiety, as if they could foresee the shadow of their impending fate. This facies is seen mostly in children between two and four years. It is not constant in all active cases, but may be the first thing to call attention to the diagnosis. (Figures 16 and 17.)



FIG. 17. W. H. Aspect of a boy of two and one-half years, weight 19 pounds. He had long lashes, lustrous eyes, thick lips and unsmling expression seen in many younger children with active disease. He had pressure on the left main bronchus from an enormous mass of tracheobronchial nodes causing absent breath sounds over the whole lung, with irregular fever. Nevertheless in three months he had gained six pounds, had no fever, good breath sounds in the left lung and was a merry, normal looking child.

Other corroborative signs are seen but are inconstant.

Hypertrichosis, or increased hair on the body, especially on the nape, arms and legs with long lashes. Increase in hair is seen also in many chronic infections, such as prolonged surgical suppuration. A familial tendency to hairiness must be discounted. The present custom of having

children wear bathing suits or sun suits much of the summer certainly seems to stimulate the growth of hair on arms and legs in some children. Nevertheless, long lashes and hairy arms and nape are often seen in children with tuberculosis which is, or has recently been active, and it is a suggestive finding.

Phlyctenules on the cornea are nearly always due to the toxins of tuberculosis. The photophobia and aspect are characteristic and may be the first suspicious signs.

Tuberculides are also significant, especially the papulonecrotic tuberculide because it represents a definite hematogenous spread. These occur on the trunk and extensor surfaces of the extremities. They are small raised lesions with a depressed necrotic center and are mistaken for chicken pox at times. They often occur in crops at long intervals.



FIG 18 J. G., 11 years. In apparently perfect health until skin eruption appeared. On the extensor surfaces of the forearms are numerous papulo-necrotic tuberculides. She had slight fever at times up to 100.5° . Roentgen-ray negative. No other foci discoverable. The Mantoux reaction to 1/10 mg. was nearly three inches in diameter. This case probably represents a small discharge of bacilli into the blood stream from a mediastinal node. All the discoverable localization at this time was in the skin.

Erythema nodosum should probably be classified as a toxic tuberculide. It was formerly thought to be rheumatic and is still reported as a common occurrence in some studies of rheumatism. It is much more often seen in

children with tuberculosis than in our large rheumatism and cardiac clinics. The tuberculin skin test is rarely negative. In one case, an attack of erythema nodosum was apparently precipitated by a Mantoux test. The appearance of the acutely red swellings on the shins is so suggestive of periostitis that the children are often sent in to the surgical wards. The tenderness is much less than would be expected from the appearance. It may be the first thing to call attention to tuberculosis, as in the case of a small girl who was recently admitted for erythema nodosum which had suddenly come on while she was in apparently perfect health. Her roentgen-ray showed a marked primary focus with beginning calcification and definite bronchopulmonary nodes in the hilus. She had irregular fever which had never been suspected. Her small brother also was found to have a primary complex. In this case the erythema nodosum was a fortunate incident for both since it led to early diagnosis.

It is obvious that this symptom complex in the older children is indefinite. Irregular fever, languor, failure to gain properly make up the triad of sig-

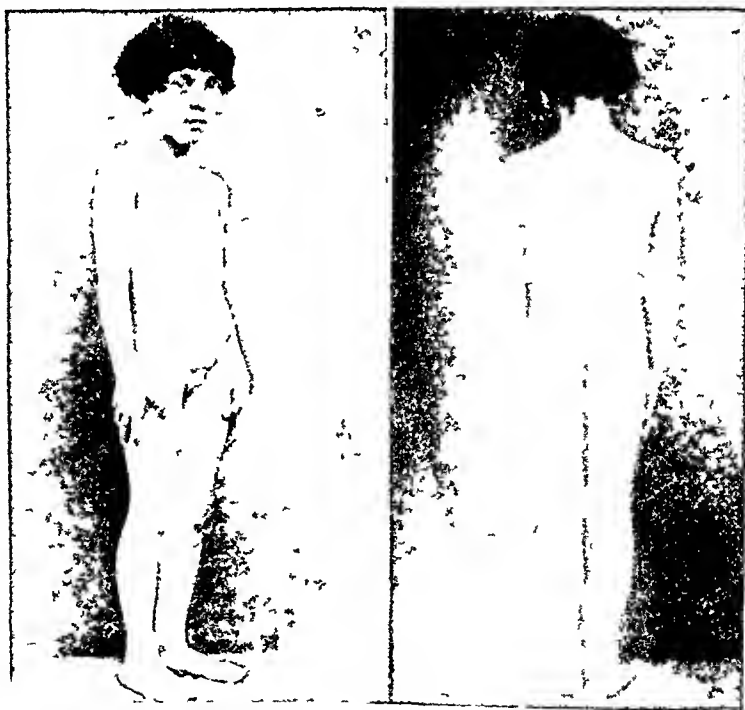


FIG 19 J B, 6 years. Mother brought her to out-patient department complaining that child was tired all the time, sitting around the house and eating little. She had lost some weight. The child was fairly nourished but had lustrous eyes, long lashes and a hairy nape. Her temperature was 100.5° by rectum. Tracheal whisper to fifth dorsal spine area indicated by white line. No abnormal signs in the lungs. The Mantoux was positive to 1/10 mg. The roentgen-ray showed a calcifying primary focus at the right base and calcification in the right hilus region. This is an example of the indefiniteness of the symptoms seen in these cases and how easily the diagnosis may be overlooked. It is even more easy to overlook active tuberculosis when the roentgen-ray is entirely negative.

nificance with or without hypertrichosis, and should always lead to further study. A Mantoux test, if positive, should be followed up by roentgen-ray study. Phlyctenules and tuberculides are more definitely diagnostic.



FIG 20 Roentgen-ray of J. B., described under figure 19. 1. Calcified primary focus. 2. Calcified bronchopulmonary nodes. Note that child still had fever and apathy, although calcification had begun.

In many cases the roentgen-ray will show little, perhaps some calcification. It may be pointed out that too much is often read into slight variations in the size and shape of the hilus shadow by many radiologists. There is considerable variation in the shape and density of these in normal children. Only large variations or definite calcification may be considered pathological. The tracheobronchial nodes are not often large enough in older children to encroach on the pulmonic fields. Small lesions may be found in the lungs, occasionally hilus infiltration. Pleural effusion is more common in older children than in infants.

Stomach washings have demonstrated tubercle bacilli, by guinea pig inoculation, in a small number of children thought to have only lymph node tuberculosis, showing that, even when there are no symptoms, small open lesions in the lungs may be present which are not recognized by roentgen-ray or physical examination.

In children approaching puberty definite apical infiltrations like those in adults are occasionally found. Children may develop definite advancing fibrocaseous phthisis exactly like that of adults. They have then the cough,

expectoration, wasting and fever, as well as the characteristic roentgen-ray findings. Care should be exercised, however, not to confuse with this type of disease the cases of non-tuberculous fibrosis with bronchiectasia more frequently seen in childhood.

Physical examination of the chest reveals nothing as a rule, nor should physical signs of the usual kind be expected except in the frank pulmonary cases. There is one sign whose value is not generally appreciated—that is the one bearing the name of D'Espine. A good deal has been written about it, but still very few medical schools teach its technic and significance. It is usually dismissed in a word as being of no importance.

D'Espine's sign deals with the transmission of the whispered voice, or the whispered concomitant heard after the spoken voice in the interscapular region. I have found the whisper more satisfactory, since the concomitant may not be present at all in a given child. The sign is elicited as follows: When a child whispers "three," or "three trees" and one listens over the cervical spinous processes a definite whisper of tracheal quality is heard. Over the lower dorsal spines the usual vesicular whisper is obtained. If the stethoscope is moved up and down it is found that there is usually a sharp line at which the transition from tracheal to vesicular whisper takes place. This line is V-shaped as a rule, the apex being at the first to third dorsal spines and thence running up and out over the root of the neck to about mid clavicle. The child should stand with the head slightly bent forward so that the cervical and dorsal spines make an even curve. D'Espine thought that any whisper or whisper concomitant below the first dorsal was abnormal and the sign has been called "positive" when below this level. Others have found that it might be as low as the third dorsal or even the fourth in normal children, so that it is better to note the exact level of tracheal whisper transmission than to use the term positive or negative.

The sign is based on the increased transmission of the whisper from the trachea to the spinal column in all cases where there is increased density of the structures in the mediastinum. Thus there is a lowered tracheal whisper transmission in mediastinal adenopathy, tuberculous or simple, in Hodgkin's disease, leukemia, pneumonia, fibrosis or tuberculosis of the lung and in spinal deformities when there is an abnormal relationship between the trachea and the spinal column.

I have used this sign on all children I have examined since 1912 when Stoll first called it to my attention. In a small series in 1921 I reported a correlation between the D'Espine and positive tuberculin reaction which seemed more than accidental. Since that time my impression of the value of this sign has been strengthened. It is not pathognomonic of tuberculosis of the mediastinal nodes. Still it is a definite physical sign which should be given the consideration of any physical sign, no more, no less. In the absence of any other causes of enlargement of the nodes, or of any cause for increasing the density of the neighboring lung, a tracheal whisper trans-

mitted below the third or fourth dorsal spine is almost certain to be associated with a positive tuberculin reaction

Percussion of the interscapular region may give a lowered upper level of pulmonary resonance, i.e., the relative dullness normally found at the apex which extends down to about the spine of the scapula, may extend lower than this if there is increased density of underlying structure. Increased significance may be attached to a lowered change in percussion note if it is associated with a low tracheal whisper, especially if both are asymmetrical. But one must not expect to discover small lesions by percussion through the spinal column and thick muscles of the back.

It is not possible or necessary to go into the clinical aspects of bone, joint or genito-urinary, skin, eye and other forms of localized tuberculosis. It is proper, however, to point out the too common mistake of making a diagnosis of tuberculosis on clinical signs alone, or even on the roentgen-ray film without so simple a procedure as the tuberculin test. I have seen this done repeatedly by general practitioners, by internists high in their branch of medicine, and by various specialists in orthopedics. Since the skin test is of smaller use in adult work, it is very easy to forget its value in children.

DIAGNOSIS

In infancy, fever, loss of weight, with or without persistent signs in the lung, should suggest tuberculosis. Of course, bone disease and meningitis always do so. A Mantoux test, the roentgen-ray and carefully recorded temperature and weight curves are necessary to complete the diagnosis.

In older children, failure to gain, languor, fatiguability, a low transmission of the tracheal whisper and hypertrichosis are suggestive. Phlyctenules, tuberculides or any local disease may be the first sign indicating the need of fuller study by a careful rectal temperature curve, Mantoux and roentgen-ray. With a positive Mantoux, fever is significant of activity even with a normal roentgen-ray.

In the diagnosis of tuberculosis three questions should always be kept in mind.

First *Has the child been infected with tuberculosis?* The answer to this is easily obtained from a properly performed Mantoux test.

Second *What is the site of the disease?* The answer may be given by the symptoms, a careful physical examination and good roentgen-ray films. All of these may be practically negative. But in this event we feel sure that the mediastinal nodes are probably the site of the disease, since they are involved in most primary infections, or secondarily to some degree even when the primary complex is elsewhere.

Third *Is the disease active, stationary, or cured?* This must be judged by general symptoms, fever, the effect on the nutrition and, of course, by any signs or symptoms of local activity if they are present.

TREATMENT

The treatment of children with tuberculosis is based on the same principles as those used in adults. If there are no local or general signs of activity a child should lead a normal life with somewhat closer watching than usual. Activity of the process as shown by fever, failure to gain or local signs of activity demands rest until all the symptoms have entirely disappeared. A rest cure on a veranda, on a roof, or in an open room should be planned with exact attention to every item in the entire day.

The diet is important and should be prescribed with care. Children do not take food nor digest it well if fed too often. Milk between meals or with meat meals is not advisable for any child. It is better to give the three simple meals which a child usually takes with bread and butter between meals. This digests and leaves the stomach in two hours and puts weight on the child better than too much milk, which stays in the stomach three to three and a half hours. The popular slogan that every child needs a quart of milk to drink every day is not based on experience with normal children and hence should not be the rule with sick ones. If a child has 10 or 12 ounces of milk at breakfast and supper and gets some cooked in his soups, desserts, and so forth, he actually receives the greater part of a quart. But if he takes too much milk he is likely to refuse other foods and so get into the habit of eating an unbalanced diet. Cod liver oil should be given for its effect on the calcium metabolism and perhaps for the protection against respiratory infections. It should be given after meals in any form the child takes best, plain, in orange juice, in emulsion or with a malt preparation. The numerous substitutes, viosterol, tablets, concentrates, etc., which are popular today, do not replace cod liver oil. Some of them may do harm from the large amounts of vitamin D contained. There is no evidence that it is desirable to give enormous amounts of this substance. The same warning holds against over-use of the ultra-violet ray.

No food should be forced, and the child should not be coaxed, amused or bribed to eat. A meal should be put before him and nothing said about it. In half an hour it should be taken away and nothing given until the next feeding, no matter what has been left. In a few days he will eat willingly.

The above is closely linked with a psychological aspect of the care of chronically sick children which must never be forgotten. Some children develop a "lime light complex" very easily and will try in every way to get attention. Under the circumstances it is very easy for a distracted mother, who has been told that her child has tuberculosis, to spoil him at any cost, fearing that he may not recover and wishing to make him happy. But spoiling never makes a child happy for long and unless a reasonable discipline is maintained it is impossible to carry out any planned regime. It is easily possible to keep any child perfectly happy for any number of years on a

complete rest cure if all this is understood at the outset and if he is never allowed to become sorry for himself. One of the essentials is a good bed table which fits across his lap on which he can play, with enough simple toys or easy lessons to keep him occupied. Without occupation no child will stay at rest.

In a planned rest cure in childhood forethought must be taken about the bowels. As a rule a mild laxative such as aromatic extract of cascara may be needed, at first at least. It should be gradually lessened in amount and an attempt made to induce a movement with high residue foods, again, mineral oil, and so forth. If the bowels do not move adequately after breakfast, a small soapsuds enema should be given at once so that the habit of a normal time for evacuation shall be maintained.

The difficult period comes when a child first begins to get up. As soon as the temperature stays under 100° for several weeks, if he is up to normal weight, and if there is no contraindication from local signs of activity, he may be allowed up a little at a time, but with care to avoid over-exercise. The effect on the temperature is the guide, as in adults. Unfortunately it is necessary to put him back to bed again and start over again if the temperature again rises as a result of activity.

Pneumothorax is much less useful in children than in adults. When a real parenchymatous lesion develops it is too often steadily progressive and dissemination through bronchi or the blood stream is frequent and serious. On the other hand the earlier stages are most amenable to treatment. As stated above, the primary complex heals and may not ever be recognized in the great majority of infected children. When an early stage is recognized through the examination of contacts, by a tuberculin test, or a roentgen-ray, or from an early tuberculide, etc., the family is to be congratulated, since these children do very well indeed if properly treated. Under good care it is rare to have serious progressive dissemination or meningitis. Even in cases of serious local lesions in bone, kidney, etc., the ability to recover completely is unbelievable. Some children who are febrile, emaciated, and who look as if they were doomed, will make a surprising and complete recovery under good care. Mention has been made of the possibility of resolution of lung lesions which cast massive shadows.

The resistance of the child, his race, economic status, and so forth, all influence the prognosis. Negroes and Puerto Ricans do badly in New York. The ability of the parents to plan and carry on a long campaign for months or perhaps years is one of the most important factors.

CONCLUSIONS

A clear knowledge of the pathogenesis of the forms of tuberculosis occurring in childhood must be kept constantly in mind when studying infected children, since they have many forms of the disease besides the primary complex.

All children are not infected and therefore the tuberculin test is a most valuable diagnostic aid

The effect of the disease on the temperature and weight curves more often suggests the diagnosis than local signs of disease in the lung

The roentgen-ray often makes a surprising diagnosis but may show very little or nothing in a child with definite constitutional symptoms

Tuberculosis is a serious disease in infants but even they usually recover from primary complex and often from secondary lesions. Older children do very well when properly handled, if the diagnosis is made early, before meningeal or serious pulmonary involvement

Since nearly all tuberculosis begins in childhood a further reduction in the death rate can probably best be effected by better understanding of the disease in children

HEMOCHROMATOSIS REVIEW OF THE LITERATURE AND REPORT OF THREE CASES *

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HEMOCHROMATOSIS, as the name indicates, is a metabolic disorder characterized by the deposition of the blood pigments hemofuscin and hemosiderin in various organs and tissues, associated with progressive interstitial fibrosis and sclerosis of the organs subjected to the abnormal deposition of pigment, particularly the liver, pancreas and spleen

In a large proportion of cases (85 per cent according to an analysis of 53 cases by Blanton and Healy⁴) the disease is accompanied, especially in its later stages, by diabetes mellitus. Most patients show a definite increase in pigmentation of the skin, due to hemosiderin and often associated with increase in melanin.

Troisier, in 1871, first described a "bronze cachexia" occurring in diabetes, and 10 years later Hanot and Chauffard¹⁵ called attention to a condition which they termed "bronzed diabetes". It is undoubtedly true that these diseases were the same as that described and named "hemochromatosis" by von Recklinghausen³⁷ in 1899.

Incidence Hemochromatosis, also known as pigmentary cirrhosis, is said to be comparatively rare, and only a few more than 100 cases have been reported in the literature. It occurs almost exclusively in males, less than half a dozen females having been reported. Nearly all cases fall within the middle-age group.

In the clinical records of over 100,000 admissions to the Johns Hopkins Hospital, Fitcher found but three instances of hemochromatosis. In 1435 autopsies at the University of Kansas Hospital,²⁰ only three cases of this disease were found, whereas at the Bellevue Hospital,⁴ New York City, only four cases of hemochromatosis were noted in 5000 autopsies. Mallory, Parker and Nye²² found hemosiderin deposits only four times in 224 cases of cirrhosis of the liver.

There have been about as many cases reported in Europe as in America, and the disease has been observed in Australia and New Zealand. Cheney⁷ describes a case occurring in a Japanese male, 35 years old, only three cases in Japanese having been reported in the literature.

Etiology The cause of the abnormal deposition of iron is not known. Alcoholism and chronic copper poisoning may be of etiological importance, although Cheney,⁷ Critchlow,⁹ and others reported cases with no history of exposure to these possible factors. It is quite possible that such conditions may exist without being elicited in obtaining the history.

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Rous and Oliver³⁰ caused hemochromatosis in animals by repeated blood transfusions, but there is no conclusive evidence of abnormal blood destruction in men. Mallory, Parker and Nye²² produced the disease in animals by feeding copper, and their experiments were later confirmed by Hall and Butt¹⁴. The latter produced pigment cirrhosis in rabbits, sheep, and to a lesser extent in white rats, resembling closely the early manifestations of hemochromatosis in man, by feeding these animals copper acetate. Moreover they found that alcohol administered in conjunction with the copper acetate not only failed to hasten or augment the production of pigment cirrhosis, but also reduced materially the storage of copper in the liver in both rabbits and white rats. They conclude that hemofuscin, which is produced in the livers of rabbits treated with copper, contains iron in a masked form. These workers found hemosiderin in the livers of the copper fed rabbits in much smaller quantity than hemofuscin and they believe the former to be derived from the latter.

Sources of copper poisoning which must be considered in discussing the etiology of hemochromatosis include the following:

- (1) Distilled liquors contaminated with copper dissolved from the copper worm of the condenser, by action of organic volatile acids
- (2) Occupations involving exposure to copper dust, such as work in brass foundries and mills, copper and brass fabricating mills, telephone line repairing, etc
- (3) Probably also acid foods, jellies, candies, etc., contaminated by copper vessels used in canning them, particularly if their reactions are strongly acid

In 1929 Funk and St. Clair¹⁵ reported a case of hemochromatosis without diabetes and they conclude it is unlikely that increased hemolysis is the cause of the iron pigmentation. These investigators believe that the rôle played by copper is secondary to an unknown etiologic agent. They furthermore raise the question as to whether other heavy metals such as zinc, manganese, and nickel might not also be retained in the tissues, as well as iron and copper.

Some authorities, notably Sheldon,³³ feel that the time taken for these deposits to accumulate is very long, and it is possible that the disease is an inborn error in metabolism, the accumulation being so slow that the characteristic clinical symptoms do not appear until middle age is reached.

Hemochromatosis occurring in a woman is reported by Hartman¹⁶. His patient was 28 years old and had had allergic symptoms (eczema of the face, and intolerance for milk and eggs). She gave a history of unusual sensitivity to cold and susceptibility to respiratory tract infections, including frequent attacks of sinusitis. Another case of hemochromatosis in an allergic patient was reported by Constan⁸. His patient was a male, 58 years of age, with a history of bronchial asthma of 25 years duration.

Howard and Stevens¹⁸ conclude that the disease may depend on some

injury to the liver resulting in hepatitis, and this in turn leads to a disturbance of the iron metabolism, so that there is a slight and prolonged retention of the iron, both exogenous and endogenous

Older writers have considered hemochromatosis a form of diabetes. We know now that pigmentary cirrhosis is one of the rarer *causes* of diabetes, and is not a *form* of diabetes. Hemochromatosis exists, in a minority of cases, with normal urinary and blood sugar findings.

Pathology The striking postmortem feature is the bronze color of the liver, pancreas, and other organs and tissues, especially after fixing in alcohol. The bronze or chocolate discoloration is due to the deposition of the blood pigments, hemofuscin and hemosiderin, the latter being an iron-containing derivative of hemoglobin. Chemically, hemosiderin is an iron albuminate in which iron is held in relatively loose combination. Several writers have noted increased amounts of copper in organs, Mallory²² reporting 10 such cases.

Tedstrom³⁶ reasons that since the iron deposits are increased in the cells normally metabolizing iron, it would seem that the initial lesion is a failure of the organs which normally take care of the products of blood destruction to do so.

Donaldson¹⁹ is inclined to believe that the primary lesion is one of damage to liver cells by an unknown toxin or toxins. This finds expression in the gradual disappearance of the liver cells, and in the production of fibrosis. In addition to those changes which characterize cirrhosis in general, the damaged liver cells are in some way affected so that the cells in question are no longer capable of dealing with iron offered to them in the normal course of events. This iron, therefore, probably derived mainly from the food, slowly accumulates in the damaged liver cells, where it gradually undergoes chemico-physical changes which result in the final appearance within the cells of coarse masses of iron pigment. This accumulation is analogous to what happens in case of fatty infiltration of the liver.

As regards the pigment in places other than the liver, Donaldson suggests that the massive deposits in the retroperitoneal glands consist of granules transferred there from the liver or other organs, and that the pigmentation in other organs, chiefly in secretory cells, varies in amount and extent of distribution in different cases and is probably dependent in some way on the degree of interference with the metabolism of iron in the liver. Hemofuscin is also present in most instances, but this derivative of hemoglobin does not contain iron in any recognizable form.

Callender⁵ believes that accompanying these pigments and as a result of their deposit, sclerotic lesions are produced in the liver and pancreas. He concludes that the accumulation of pigment in the liver cells leads to their destruction and replacement by proliferation of the periportal connective tissue, thus giving rise to cirrhosis of the liver. In a similar manner, cells of the pancreas and other involved organs are destroyed and replaced.

Diabetes mellitus is found to exist in the majority of cases of hemo-

chromatosis, but is absent in some. When the pigmentary cirrhosis involves the pancreas to such a degree as to impair the function of the islets of Langerhans, diabetes mellitus is added to the picture.

Increased pigmentation of the skin is not always present, but is found in most cases. It is thought to be dependent more on interference with adrenal function than on deposits of iron in the skin, although both undoubtedly play a part. A severe degree of adrenal impairment may produce a picture which suggests Addison's disease, just as the pancreatic lesions may result in diabetes.

Sheldon,³³ reporting his study of a moderately advanced case of hemochromatosis that came to autopsy, found excessive deposits of iron in all tissues examined, except the blood, which contained slightly less than the normal amount. This seems to indicate that the essential feature of this metabolic disorder is an increased avidity of the tissues for iron, which slowly accumulates in the cells in a form which they are incapable of excreting. He believes the pigment originates in the cells and is not carried to them by the blood stream from the liver and other places where it is present in exceptional amounts. He found that the central nervous system had nearly three times the normal amount of iron, but this excess was not demonstrable by the ordinary staining methods. It is believed that in cases in which large excesses of iron are demonstrated in the central nervous system by the usual staining methods, the deposits represent a later stage of the same process.

In Sheldon's case, as in one of the cases here reported, the pituitary gland was definitely involved. In his case abundant pigment was noted particularly in the anterior lobe, where it was almost entirely intracellular. It was exceptionally pronounced in the large oxyphilic cells. The pigment tended to occur around the margin of the cells rather than around the nucleus. Pituitary pigmentation was also noted by Wilson and Weiser.³⁸

In health, the body contains about three grams of iron, but in advanced cases of hemochromatosis the liver alone has been found to contain as high as 38 grams. Yet, with all this accumulation of iron-containing blood pigment, there is no evidence of abnormal blood destruction in most cases. Anemia is sometimes present, especially in the late stages, but it is not a prominent feature, and is usually attributable to some complicating condition. One of the cases here presented showed aplastic bone marrow at autopsy, and the progressive anemia developing toward the end of the disease was apparently attributable to defective hematopoiesis rather than to increased blood destruction.

Symptoms, Course and Prognosis. General weakness, malnutrition and gastrointestinal disturbances are frequent complaints. Blanton and Healy,⁴ in their analysis of 53 cases, noted that ascites occurred in about one-third of the patients and that glycosuria was present at some time in 85 per cent of cases. In 61 per cent of patients the spleen was not palpable. The skin pigmentation attracted attention in only about half of the cases.

The symptoms of cirrhosis of the liver, usually hypertrophic, or of diabetes, may be the first indications of ill health. Moeller and Hutton²⁷ report in detail a case occurring in a woman 53 years old, and lay emphasis on the extreme sensitivity to cold displayed by this patient during the course of her disease. She was not diabetic and had no clinically demonstrable cirrhosis of the liver.

The disease usually develops insidiously and the course is protracted. When diabetes does occur, it is a feature of the later stages. Krall and Ginsberg²⁸ found the average duration of life after glycosuria is discovered to be one year.

Critchlow's⁹ patient had a bronzed skin for many years, and finally sought hospitalization with symptoms of severe diabetes without acidosis. The blood sugar on admission was 400 mg. Insulin was given in doses of 15 units a day. In three days the blood sugar was reduced to 200 mg., and still there was no acidosis. The abdominal distention and ascites increased, however, and he died a non-diabetic death on the twelfth day.

Esmonde Smith³⁴ reports a rapidly progressive case of hemochromatosis with diabetes. The symptoms were of only two weeks' duration. The skin had a leaden hue, but the patient's relatives had noticed no change in his color prior to onset of his symptoms. This patient had apparently been in excellent health and was employed up until two weeks before his death. Such rapidly fulminating cases are exceptional, however, and one feels impelled to assume that the underlying disorder is slow in its development. In most instances, the disease is chronic and slowly progressive to a fatal termination.

Diagnosis Pigmentation of the skin, hepatic cirrhosis and diabetes mellitus are considered the diagnostic triad of hemochromatosis. Where such a combination of clinical findings exists recognition should not be difficult, but because of the rarity of this metabolic entity, clinicians are apt to overlook one or two of the triad components and label a case either cirrhosis of the liver, or diabetes mellitus. Furthermore, the skin pigmentation is not always apparent, nor is diabetes a constant or necessary feature of the disorder. The author believes that the most important diagnostic clue is the color of the skin, as the three cases here reported were suspected because of their peculiar complexion.

The skin has been variously described as dark brown, leaden, blue-black, and grayish-brown. It is usually a brownish slate color, not typical of the pigmentation of Addison's disease, nor is it the grayish slate color of argyria, but a shade somewhere between the two. In none of the three cases here described, with the possible exception of the fatal case, was the skin discoloration very pronounced, yet the odd, sallow complexion suggested the correct diagnosis during life. The diagnosis is firmly established by repeatedly finding hemosiderin in the urine, or by the presence of hemosiderin in an excised piece of skin.

The apparent difficulty of clinical recognition is indicated by the statement of Mills²⁶ that in 17 pathologically advanced cases, only two were recognized during life and the diagnosis proved by the demonstration of hemosiderin in an excised piece of skin

Cheney's⁷ case, occurring in a Japanese, did not have diabetes and curiously enough, despite his racial color the diagnosis was suggested by pigmentary changes in the skin

Addison's disease, argyria, and diseases producing jaundice must be considered in the differential diagnosis. The latter conditions are at times baffling, as jaundice not infrequently accompanies the cirrhosis of hemochromatosis and leads one to overlook the concomitant pigmentation of the skin which is due to the abnormal deposition of melanin, hemofuscin and hemosiderin

Treatment As chronic overindulgence in alcohol is an accepted etiologic factor, prophylaxis should include avoidance of alcoholic excess. A similar warning to avoid possible copper poisoning may be wisely heeded. The treatment of the disease, largely symptomatic, is the treatment of hepatic cirrhosis and if present, of diabetes. Regarding the latter the usual therapeutic measures may require modification and caution in administration

Callender² invites attention to the fact that in these cases of "bronzed diabetes" insulin should be used with extreme care, as the protective glycogenic activity of the liver cannot be depended upon to mobilize glycogen normally. Rapid and extreme reductions in blood sugar may thus result from the use of insulin and give rise to serious symptoms

The diabetic phase of Critchlow's⁹ case responded satisfactorily to small doses of insulin, 15 units a day, but his patient died of hepatic insufficiency 12 days after admission to a hospital. On the other hand Constam's⁸ patient, having reached a diabetic stage, was remarkably refractory to insulin. Instead of being susceptible to hypoglycemic reactions, this patient required as high as 300 units in one day to reduce the hyperglycemia. It would be interesting to ascertain whether this man was refractory to insulin only when in a state of acidosis, or whether large doses were continually ineffective

Moeller reports a case in a woman showing no diabetes and no clinically demonstrable liver cirrhosis. She obtained distinct benefit from the following medication: pituitary (ant lobe) 2 grams, suprarenal (whole gland) 1 grain, strychnia 1/60 grain. Capsules containing this mixture were ingested three times a day. Two years later, when her case history was published, she was still maintaining her improvement

CASE REPORTS

Three cases of hemochromatosis were observed on the Medical Service of Walter Reed General Hospital within the last 12 months. The patients

underwent thorough survey in hospital, but only significant or pertinent findings are herewith abstracted from their clinical records *

CASE I

A white male bachelor, aged 52, retired army officer, was admitted to Walter Reed General Hospital May 25, 1932. His family history was negative.

Personal History He admitted moderate indulgence in alcoholic liquors until two years ago. His history included the usual childhood diseases and also scarlet fever with left otitis media and subsequent faulty hearing and occasional slight aural discharge. He had had pneumonia as a child and again in 1899, mild typhoid fever in 1898, mild dengue fever twice, herniotomy in 1917, tonsillectomy in 1920 and again in 1929, appendectomy in 1930.

Present Illness His complaint on admission was of pain in metacarpal-phalangeal joints of middle and index fingers of the right hand, a condition which had bothered him for the past 13 years and for which he had undergone repeated treatment and surveys for focal infection. When operated upon for acute appendicitis in 1930 an enlarged liver was found and believed to represent Hanot's cirrhosis. This patient has since noted that his color is "pasty" and that he has gradually developed a discoloration of the skin of the lower half of both legs, without swelling. For many years his skin has been dry and lusterless, especially on the extensor surfaces of limbs. He has a tendency to sleep a good deal and is somewhat drowsy during the day. There has been long standing loss of libido and potentia.

Physical Examination The patient was a fairly well muscled and nourished male, 66 inches tall and weighed 125 pounds (five pounds under his usual weight). The skin was dry, slightly thickened and doughy, and complexion muddy. There was a grayish-brown pigmentation of the skin of the lower half of each leg. Slight varicosities of the veins of the lower extremities, but no edema. The blood pressure was 138/78. The testicles were atrophic, liver enlarged and firm, four fingers' breadth beneath costal margin, not tender, spleen palpable, some pain on extreme motion of metacarpal-phalangeal joints of index and middle fingers, right hand. Physical examination was otherwise essentially negative.

Röntgen-Ray Examinations Slight narrowing of interphalangeal joint spaces of both hands was noted. Stereoscopic plates of the skull showed the sella to be small and apparently completely closed. The gastrointestinal series revealed no organic abnormality, although the lowest point of the greater gastric curvature in the upright position was on a level with the anterior superior iliac spine. The first portion of the duodenum while diminutive and somewhat spastic shows no constant defect. There was a small calculus, 5 cm. in diameter, in the gall-bladder.

Laboratory Findings Six urinalyses were negative except for trace of albumin in one specimen. Concentration test indicated mild renal impairment, but the phenol-sulphonaphthalein test showed elimination of 75 per cent of the dye in two hours. Urine negative for hemosiderin. Examination and culture of feces showed no blood, parasites, ova, or *Streptococcus hemolyticus* or *viridans*, but a small green-producing coccus and a larger gram-positive coccus were isolated, and an autogenous vaccine prepared. The differential blood picture was normal. The red blood cell count was 4,000,000-4,130,000, white blood cells 5,500-6,500, Hgb per cent, 65-75, polymorphonuclear neutrophils 50-54 per cent. Wasseimann and Kahn tests were

* Acknowledgment is made to Major J. R. Hudnall, M.C., for his clinical study of Cases 1 and 2, to Captain Ray H. Skaggs, M.C., for his clinical study of Case 3, and to Major Hugh Mahon, M.C., for his postmortem study of the pathology in Case 3.

The photomicrographs were made at the Army Medical Museum. Acknowledgment is made to Major Virgil Cornell and to Major Raymond Dart of the Army Medical Museum, for their further study and illustration of the pathologic material in these cases.



Fig 1 Case 1 Hemochromatosis
the derma is indicated
by arrows, increased mastocytes in
derma, iron stain $\times 700$

negative Blood chemistry urea nitrogen 12.04 mg, sugar 115.6 mg, and chlorides 511.5 mg per 100 c.c. Glucose tolerance test fasting blood sugar, 122.7 mg, half-hour, 200 mg, 1 hour, 243.8 mg, 2 hours, 235.3 mg, and 3 hours, 190.4 mg per 100 c.c. The urine was negative for sugar in the first three specimens and positive in the last two. Five estimations of the basal metabolic rate between May 27 and July 4 varied from minus 30 to minus 5 per cent. Free HCl was absent in the fasting stomach, but was present after a test meal. Microscopic examination of a piece of skin removed from the right leg showed diffuse pigmentation of the derma by iron-containing pigment, compatible with a diagnosis of hemochromatosis.

Progress Autogenous vaccine prepared from streptococci isolated from feces was administered, physiotherapy continued, and thyroid and pituitary therapy instituted. Progressive improvement was noted and the patient left the hospital July 26, 1932, feeling that he was in better health than he had been for years. He was advised to continue diet, autogenous vaccine, thyroid and pituitary therapy.

Diagnoses (1) arthritis, chronic, infectious, moderate, with atrophic changes, first metacarpal-phalangeal joint, right, and first metatarsal-phalangeal joint, left, and slight atrophic changes, interphalangeal joints, both hands, (2) hemochromatosis, moderately severe, (3) pituitary gland, anterior lobe, hypofunction of, postadolescent, cause undetermined.

Comment The diagnosis of hemochromatosis in this case is based on the following findings: (a) a hard, hypertrophic liver, (b) bronzing of the skin, with demonstration of hemosiderin on laboratory study, (c) definitely diminished glucose tolerance, as demonstrated by a diabetic blood sugar curve following glucose tolerance test, with glycosuria during the test, (d) slight enlargement of the spleen.

The diagnosis of pituitary insufficiency is believed warranted because of the apparently completely closed sella, atrophy of genitals with long-standing impotence, lowered basal metabolic rate, and dry, thickened skin. These latter findings might be properly interpreted as due to thyroid insufficiency, but the composite picture is rather one of pituitary disease (anterior lobe deficiency) with secondary thyroid hypofunction. The question arises as to what role, if any, the pituitary hypofunction played in the development of hemochromatosis in this case.

CASE II

A white, married, male physician, 40 years old, was admitted to the Walter Reed Hospital December 12, 1932. His family history was negative.

Personal History There was nothing of importance noted except liberal indulgence in strong alcoholic liquors for many years.

Present Illness This patient had been in good health until about December 1, 1932, when he noticed that his feet seemed swollen. This swelling increased in amount, gradually ascending both legs, until about December 5 it reached his waist. Then he noted that his abdomen was getting larger. He stated he had had no other symptoms, but that about eight months before for some unaccountable reason, he had lost 40 pounds in weight (from his usual weight of 220 pounds). He was 70 inches tall, and had remained at about 180 pounds during the past eight months. On admission to the hospital he complained of swelling of feet, legs and abdominal wall, and of pressure in abdomen which became embarrassing to respiration. He remembered no symptoms suggestive of cardiac or renal disorder, nor any digestive disturbance until present swelling. At the time of examination he had abdominal discomfort and severe diarrhea.

Physical Examination This patient was getting about in a wheelchair and was slightly dyspneic. There was marked edema below the knees and edema of back and abdominal wall. The skin had a brownish leaden hue most pronounced on the face, which exhibited also a slight dirty brownish mottling. The radial, brachial, and



Fig 2 Case 2 Hemochromatosis Granules of iron pigment in histiocytes along the course of a small vessel in the dermis Iron stain $\times 700$

retinal vessels were moderately sclerotic. The blood pressure was 130/68. Excursion of the lungs was limited by upward thrust of diaphragm due to ascites. The abdomen was distended, the greater prominence seeming to be above the waist, giving the impression of a tumor. Palpation for liver and spleen was unsatisfactory because of ascites. The right upper quadrant was slightly tender, but no masses were anywhere palpable. The superficial veins of the abdomen were enlarged. Bilateral mucosal ulcerations were seen on nasal septum. The sclerae were moderately icteric. *Roentgen-Ray* of the chest revealed abnormally high diaphragm, enlargement of hilus and increased root branch markings, but no infiltration or consolidation.

Laboratory Findings Fifteen urinalyses were negative except for albumin in one of them and rarely a granular cast. Specific gravity range was between 1.009 and 1.026. Four specimens were examined for hemosiderin, and all were positive. Feces showed occult blood, but no ova or parasites. Red blood cell count, 3,330,000, white blood cells 13,000, Hgb 75 per cent, polymorphonuclear neutrophils 77 per cent. Blood Wassermann and Kahn tests negative on three examinations. Blood chemistry: urea nitrogen 16.66 mg, sugar 113.6 mg per 100 c.c. Culture of ascitic fluid yielded no growth. Blood icterus index 25. Examination of one section of skin for hemosiderin was negative, but subsequent examination of another section of the same biopsy specimen was positive.

Progress Following abdominal paracentesis, an enlarged, hard liver could be palpated, but the spleen could not be felt. Residual ascites interfered with examination. Soon after admission a severe psychosis developed, which proved to be delirium tremens, and which cleared under treatment in close confinement. Abdominal paracentesis and diuretics resulted in marked reduction of the ascites and edema. At the time of his discharge from the hospital, January 27, 1933, he was much improved, ambulatory, and entirely recovered from his alcoholic psychosis.

Diagnosis (1) psychosis, acute, alcoholic, delirium tremens, moderately severe, (2) hemochromatosis, moderately severe, (3) arteriosclerosis, generalized, moderately severe.

Comment The diagnosis of hemochromatosis in this case is believed warranted by the following findings: (a) hypertrophic cirrhosis of the liver, with ascites, (b) laboratory demonstration of hemosiderin in all urines examined for this pigment (four specimens), (c) increased pigmentation of the skin, with hemosiderin found in the one piece of excised skin. (The biopsy specimen was obtained from the leg, where pigmentation was not pronounced and lacked the grayish-brown color seen in his face.)

Diabetes was not present in this case, although a blood sugar tolerance test was not done. As with most reported cases of hemochromatosis, protracted excessive ingestion of alcohol was a noteworthy feature.

CASE III

A white married male, 41 years old, a soldier for the past 20 years, was admitted to the Walter Reed Hospital November 14, 1932. His family history was negative, and he had no children.

Personal History He had had the usual childhood diseases, malaria in 1914, dysentery in 1914 (type unknown), sciatica for several years prior to tonsillectomy in 1928. He acknowledged excessive indulgence in alcohol over a long period of years, but claimed to have given it up the year before because of digestive disturbances which it aggravated.

Present Illness Since dysentery in 1914, he has been subject to frequent attacks of indigestion manifested by severe flatulency, vomiting, frequent sour eructations, and alternating constipation and diarrhea. He drank heavily prior to 1932, but found that drinking aggravated his digestive symptoms. These gastrointestinal dis-



FIG 3 Case 3 Hemochromatosis Section of liver showing iron pigment deposits

turbances have been getting rapidly and progressively worse since January 1932, and he has lost about 25 pounds in weight. He was under observation in this hospital from September 9 to September 13, 1930, because of acute alcoholism, and again from April 27 to June 15, 1932 with a diagnosis of chronic catarrhal gastritis. He had three non-vital teeth with extensive periapical resorption which he was advised to have extracted at his station, but this has not been done. Some improvement was maintained until October 10, 1932, when diarrhea developed (7 to 8 stools a day) with moderate tenesmus, but no blood or mucus was noticed.

On November 14, 1932, he awoke during the night with sharp pain in upper abdomen, which radiated behind the lower sternum. He noticed a slight dry cough and found that deep inspiration increased pain, which he thought was due to gas on stomach. An enema brought slight relief, but the pain persisted and he was sent to this hospital that morning.

Physical Examination This patient was ambulatory and without fever but appeared to be in acute pain. His height was 65½ inches and weight 104 pounds, about 31 pounds under his usual weight. The skin showed marked increase in brown pigmentation, to which was added a slight leaden hue. The tongue was red, with a few superficial ulcerated areas. The blood pressure was 98/62. The abdomen was flat, firm, tympanitic in upper portion, and slight epigastric tenderness, but no masses. The liver was not enlarged and spleen not palpable. Dental focal infection was noted in three teeth. The nasal septum was deviated to left, but the sinuses were clinically normal. The tonsils were out, but hyperplastic tissue was seen in left fossa. The eyes were negative except for small amount of white exudative material in both physiological cups, suggestive of old optic neuritis. *Electrocardiogram* showed sinus bradycardia with slight sinus arrhythmia and P-waves of very low amplitude in all leads, but no definite evidence of cardiac disease.

Röntgen-Rays Gall-bladder failed to visualize, although in May 1932, during a previous admission, it was normal. Gastrointestinal series and barium enema show nothing abnormal. A chest film and flat film of abdomen negative.

Laboratory Findings Urinalyses were negative. The one specimen examined for hemosiderin was negative. Section of excised skin examined for hemosiderin also reported negative. Examination of feces revealed neither parasites nor ova. Cultures of stools were negative for *Endamebac histolytica* and for the typhoid-dysentery group. No tubercle bacilli were found in the sputum. On admission, the red blood cells numbered 3,420,000 with 70 per cent hemoglobin, but this steadily decreased until on February 18, 1933, there were 1,220,000 red cells with 40 per cent hemoglobin. The differential count was not remarkable and the smear negative for malaria. On November 15, 1932, the blood Wassermann test was reported plus-minus, and Kahn test single plus, but on recheck November 19, 1932, both were negative. Blood chemistry: urea nitrogen 14.42 mg, glucose 90.9 mg, per 100 c.c. blood. Van den Berg negative. Blood icterus index 4.2. Basal metabolic rate plus 8 per cent. The glucose tolerance test gave a peculiar reading which was interpreted as failure of sugar absorption from the alimentary canal: fasting sugar 100.5 mg, at the half hour 90.9 mg, at 1 hr 88.8 mg, at 2 hrs 102.5 mg, at 3 hrs 100 mg per 100 c.c. blood, urine negative throughout the test.

Progress A few days after admission, the blood pressure rose to 134/72, but slowly declined until on March 7, 1933, when practically moribund two days before death, it was 60/30. Addison's disease, hidden neoplasm, atrophic cirrhosis of liver, and hemochromatosis were all suspected in this case. The patient received treatment with Eschatin (P. D. & Co. preparation of adrenal cortical extract) and with cortin manufactured by the Army Medical School, with distinct temporary improvement. Restriction of this adrenal cortical extract resulted in rapid and severe relapses. These therapeutic tests convinced observers that the patient's life was prolonged by the administration of this substance. Death occurred March 9, 1933.

Diagnosis Although hemochromatosis was suspected in this case, a clinical diagnosis was not warranted, in view of failure to demonstrate hemosiderin in either the specimen of urine or skin section submitted for such examination. Therefore clinical diagnoses were rendered as follows: (1) Addison's disease, (2) bronchopneumonia, acute, terminal, both lower lobes, (3) enteritis, subacute, ulcerative, cause undetermined.

Autopsy Findings The liver weighed 1150 gm, its capsule was smooth, color dark red, and edges sharp. The cut surface was much darker than normal and markings were almost obliterated. The pancreas weighed 90 gm, colored a peculiar reddish-brown both through its capsule and on section. The spleen weighed 110 gm, its capsule was slate color. The cut surface paler than usual and the pulp difficult to remove by scraping. The adrenals were small and on section, the cortices were pale yellow and narrow, the medullae were a dirty dark brown and diffuent.

Anatomical Diagnoses (based on gross and microscopic postmortem findings) (1) hemochromatosis, (2) bronchopneumonia, acute, terminal, hypostatic, lower lobes, both lungs, (3) cirrhosis, atrophic, pigment, of liver, (4) pigment (iron) deposition in liver, (5) pigment deposition (lipochrome, "wear and tear") in heart, adrenals, testes, intestine, and pituitary, (6) brown atrophy of heart, (7) enteritis, chronic, ulcerative, of ileum, cause undetermined, (8) emaciation and skeletal muscular atrophy, (9) aplastic bone marrow, (10) pleuritis fibrinous, bilateral, slight, (11) decubitus, sacral, (12) atrophy of testicles.

COMMENT

There was much less clinical evidence of hemochromatosis in this case than in the first two cases, but postmortem examination proved conclusively the existence of this disease. A pathological diagnosis of Addison's disease was not made, and it is questionable whether the composite picture justifies such a diagnosis. Adrenal insufficiency unquestionably existed, but it is debatable whether or not the hemochromatosis was responsible for the clinical picture of Addison's disease (not limiting the latter term to a tuberculous infection of the adrenals). This case suggests that hemochromatosis may be a rare cause of Addison's disease, just as hemochromatosis may be a rare cause of diabetes. Abnormal deposition of iron pigment was not demonstrated in either the adrenals or pituitary in this case. However, the question arises whether the iron pigment might not have been present in those structures in masked form, not demonstrable by the usual staining reactions. Sheldon³³ found such excess of iron in the central nervous system of his case, not demonstrable by ordinary staining methods.

SUMMARY

Three proved cases of hemochromatosis, recognized on the Medical Service of the Walter Reed General Hospital within a period of 12 months, arouse suspicion that the disease is not as rare as the literature indicates.

Two of these cases were recognized clinically, and were discharged to their own care after reaching maximum hospital benefit. The third case progressed to a fatal termination in hospital and, while the diagnosis was suggested, because of failure to demonstrate hemosiderin in either urine or skin it could not be proved until autopsy.

The generally accepted diagnostic triad includes (a) grayish-brown pigmentation of the skin, (b) cirrhosis of the liver (sometimes atrophic, but usually hypertrophic), (c) diabetes mellitus. This triad need not be observed to establish a diagnosis. The diabetes may be lacking, dependent on the degree of pigment (iron) degeneration and fibrotic replacement of islet tissue in the pancreas.

The skin pigmentation, which is not always observed, is due partly to the deposition in the skin of an iron-containing derivative of hemoglobin, hemosiderin, and partly to an increase in the normal melanin of the skin. It is believed that the increased melanin may be incident to adrenal impairment brought about by fibrotic changes.

Pigmentary cirrhosis of the liver is the one constant feature of this disease. Splenic fibrosis with moderate enlargement is usually present, but not always demonstrable clinically.

Pituitary involvement was found in two of the cases here reported (Cases 1 and 3) but was not searched for in Case 2. The two patients in whom pituitary involvement was demonstrated also had bilaterally atrophic testicles.

The history of immoderate indulgence in alcohol in these three cases supports the views of other writers that alcoholism is in some way an important etiologic factor. No history indicative of copper poisoning was elicited from these patients.

CONCLUSIONS

1 Hemochromatosis is not a form of diabetes, as was thought by the older writers, but is one of the rarer causes of diabetes mellitus. Few cases of diabetes are caused by the much rarer hemochromatosis, but the latter disease usually does cause diabetes sooner or later.

2 Addison's disease may be simulated by the skin pigmentation, or adrenal insufficiency may be a real complication of hemochromatosis, dependent on pigmentary fibrosis of the adrenals.

3 Pituitary (anterior lobe) insufficiency may be an etiologic factor, but it is more likely a complication of hemochromatosis dependent on pigmentary fibrosis of the hypophysis, and is more prone to occur in patients with small sellas or otherwise exhibiting tendency to pituitary hypofunction.

4 To promote more widespread recognition of this disease, hemochromatosis should be considered in every case of diabetes mellitus, every case of cirrhosis of the liver, and every case of abnormal pigmentation of the skin. The diagnostic triad is encountered rarely, it is true, and even then its significance may be overlooked.

5 Some investigators have shown that copper poisoning is one cause of hemochromatosis. This should be borne in mind when prescribing copper therapeutically, as is so frequently done in combination with iron. It has been assumed that in copper therapy the mobilization of iron for hemoglobin building is facilitated. If also, as a result of copper therapy, elimina-

tion of iron is retarded and deposition of iron in the tissues is augmented, copper may not be so beneficial as hitherto believed. It is quite possible, however, that in the therapeutic dosage in which it is used in the treatment of anemia, copper exercises no such deleterious effect.

6 More careful research is indicated concerning the action of copper and iron, the effect of the former on hematopoiesis, and to determine whether, in therapeutic dosage over long periods of time, it may produce pigmentary cirrhosis.

7 Until more conclusive experimental and clinical facts are available, caution should be exercised in the dosage and continuity of administration of the various copper-and-iron compounds which now are enjoying such popularity.

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PHILADELPHIA AND AMERICAN MEDICINE

THE approaching annual meetings of the American College of Physicians, to be held in Philadelphia, will bring the members of this College back to the cradle of organized medicine in this country. If a cradle were all that the city of Philadelphia had to offer the visiting physician, it is obvious that the meetings would, in all probability, have been scheduled elsewhere. The truth in our case is, of course, that today Philadelphia's physicians welcome their colleagues not to a city of the past, but to one into which the destiny which broods over cities has breathed a timeless and unquestioned devotion,—that towards the art of medicine.

Philadelphia, in size the third city of the country, vies with Chicago for first place in the number of recognized medical schools, each having five. The statistics on hospitals and physicians in the three cities are approximately in proportion to their population.



*Your ever affec^d Brother
John Morgan*

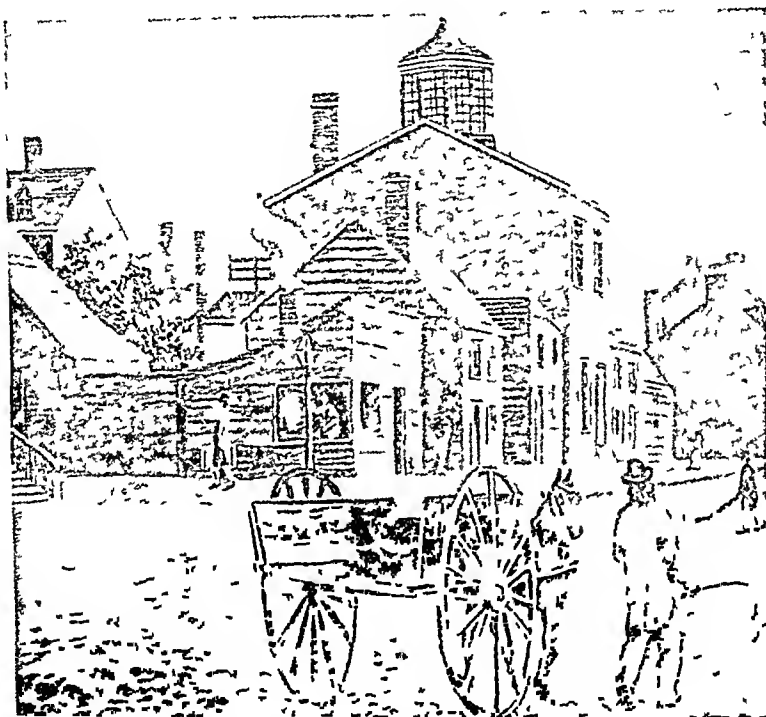
DR. JOHN MORGAN, 1735–1789 A.B. 1757, College of Philadelphia, M.D. 1763, Edinburgh

The Medical School of the University of Pennsylvania * in September of this year, holocaust and taxes not intervening, will undertake for the one hundred and seventieth year to offer organized medical instruction to the youth of this and other lands. The record is unique in this country. This first medical school in the colonies came into being in 1765 as the Department

* The following material has been assembled and in large part taken verbatim from the Reports and Announcements and from individual histories of the various institutions.

of Medicine of the College of Philadelphia, largely through the efforts of a distinguished Philadelphia physician, John Morgan, who, appropriately, was elected to the first medical professorship in the colonies. Morgan belonged to that first great group of Philadelphia physicians whose superb vigor of mind and body, and whose devotion to the progress of American medicine, left their impress indelibly upon the face and in the soul of the city.

On June 21, 1768, ten students walked out of the commencement exercises of the College of Philadelphia (now the University of Pennsylvania), with the first medical degrees granted by the first medical school in the country. Since that day, 16,366 other youths have followed in their footsteps.

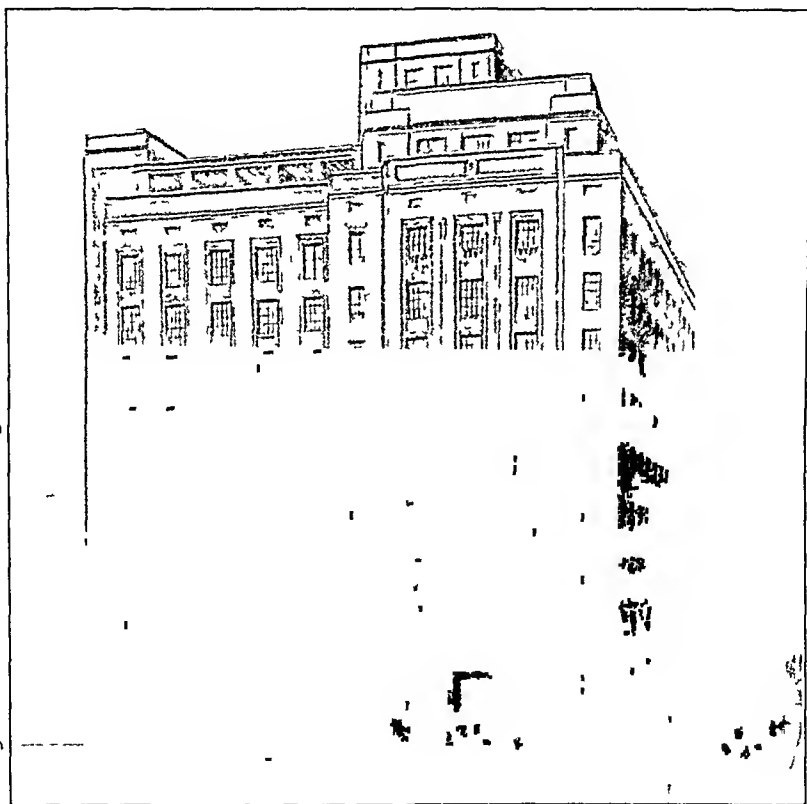


MEDICAL SCHOOL OF THE UNIVERSITY OF PENNSYLVANIA (SURGEONS' HALL), 1765-1802
(East side of Fifth Street, between Liberty and Walnut Streets)

The buildings that have housed the Medical School have been several, the catalogue of professors is long and illustrious. Over the earlier homes it would not be profitable at this time to pause. From the list of professors, piety and affection demand that we single out at least the names of William Shippen, Jr., Benjamin Rush, James Woodhouse, Benjamin Smith Barton, Caspar Wistar, Nathaniel Chapman, Philip Syng Physick, William P. Dewees, William Edmonds Horner, Robert Hare, George B. Wood, Hugh Lenox Hodge, Joseph Leidy, D. Hayes Agnew, William Goodell, William Pepper, Alfred Stillé, William Osler, Richard A. F. Penrose, H. C. Wood, Leonard Pearson, C. L. Leonard, John Ashhurst, George W. Norris, Louis Duhring, J. William White, George A. Piersol, and E. T. Reichert.

of its medical school There are at present available in it 457 ward beds as well as 98 private and 38 semi-private beds During the fiscal year of 1933 to 1934, there were 9,368 bed patients, 103,410 visits to the out-patient departments, and 7,879 surgical operations were performed Students of all four classes are taught here every clinical subject

This medical school, in brief, in the course of nearly 170 years of active life has met with amazing resource and courage the demands of our increasingly complex civilization, so that today its equipment enables it to offer its students every advantage of theoretical, practical, and research study Age has indeed not withered, nor custom been allowed to stale



GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

The University's Graduate School of Medicine, located at Nineteenth and Lombard Streets, was organized in 1916 by a merger between the University and the old Medico-Chirurgical College of Philadelphia, which had been founded in 1881 In 1918 the Philadelphia Polyclinic and College for Graduates in Medicine merged with the Graduate School of Medicine and formed the Polyclinic Section Later additions of assets included the Diagnostic and Howard Hospitals, and the North American Sanatorium

The Graduate School of Medicine today is, administratively, a separate university unit, or association of units, operating in complete cooperation with the School of Medicine, and, like the latter, is administered ultimately by the University's vice-president in charge of medical affairs. Its students are suitably qualified physicians who become, substantially, academic, clinical, or research assistants or understudies of the members of the faculty in medical activities throughout the city, intramurally and extramurally. For an essential feature of the Graduate School's "Pennsylvania Plan" of graduate medical education is the upbuilding of an extensive cooperation between the central organization, that is, the Graduate School, and extramural medical organizations and their staffs. At present, 50 of Philadelphia's medical organizations are found to be thus cooperating. The Graduate Hospital, covering more than one city block, is the clinical teaching center of the school. Its approximate normal monthly activity rate is 10,000 bed days, 600 operative cases, and 12,000 out-patient visits. The Graduate School of Medicine of the University of Pennsylvania is today the only institution of its kind in Philadelphia.

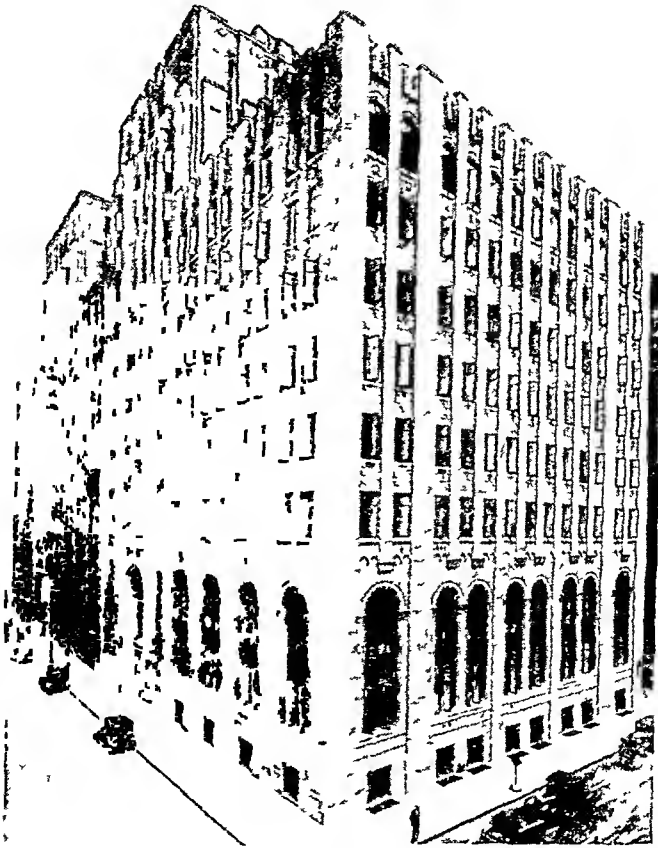
Jefferson College and Hospital Philadelphia's second medical college, in point of time, is an equally vigorous ancient of the second generation. This is the Jefferson Medical College, founded in 1825, as the Medical Department of the Jefferson College of Canonsburg, Pa. Its first class was graduated in the following year. In the intervening 108 years, it has conferred a medical degree upon approximately 16,000 of its students, a number not far short of that produced by its older sister.

The College today occupies a handsome building on Walnut Street, just west of the old College building at Tenth and Walnut Streets, where now is situated its Curtis Clinic. The College building, opened in 1929, represents, like the Maloney Pavilion of the University of Pennsylvania, a thoroughly modern response to the technical developments of the day as they affect the equipment for medical instruction and research. Herein are contained, in addition to administrative offices, professors' rooms, work rooms, recitation, lecture, demonstration, and assembly rooms, laboratories large and small, for the use of the various departments, a library, and the College Museum.

The Jeffersonians may claim that systematic clinical methods of instruction were first inaugurated, as far as the United States is concerned, within the walls of their college, since a dispensary was therein established in advance of the opening session, and it was from cases which it supplied, that Dr. George McClellan, a leading surgeon and teacher of his day, and the founder of the College, conducted the first surgical clinics in the country.

The clinical teaching is today carried on largely in the College's Hospital, adjacent to the College itself. This building, opened in 1907, with a capacity of about 377 ward beds, in addition to the private rooms, offers every facility for this purpose. Under the supervision of professors and experienced instructors, students are required to participate in operations and to assist in the administration of anesthetics. When the interests of the pa-

tient are not thereby jeopardized, the student may follow the case from admission to discharge



CURTIS CLINIC OF THE JEFFERSON COLLEGE AND HOSPITAL, WALNUT AND TENTH STREETS, WITH THE COLLEGE BUILDING AT THE LEFT

The Curtis Clinic, adjoining the College, and conforming to it architecturally, is the out-patient unit. The building is planned so as to group the various medical, surgical, and specialty divisions. The Hospital's central location insures an exceptionally large service demand, particularly in the out-patient department. The surgical division of this department received in the year ending May 31, 1933, 115,757 visits and the medical division, 90,706, giving a total out-patient service of 206,463 visits.

In 1924 the Samuel Gustine Thompson Annex to the Jefferson Hospital was opened. This building contains the teaching clinical amphitheater, seating 550, a maternity department, bronchoscopic wards, and a teaching clinical laboratory upon the roof. The Department of Anatomy, including Descriptive and Practical Anatomy, Histology and Embryology, and

Anatomy as applied to Medicine and Surgery, is housed in a building of its own at Clinton and Eleventh Streets, a few blocks from the College. This is the Daniel Baugh Institute of Anatomy, containing laboratories, a museum, amphitheaters, and a notable departmental anatomical reference library. The Department for Diseases of the Chest is likewise set apart, in a building at 238 Pine Street. Although the activities here are concerned largely with the problem of tuberculosis, other related conditions are studied and treated. Twelve students are selected from the fourth year class to reside in the department and assist in the preparation of histories and in the special study of patients.

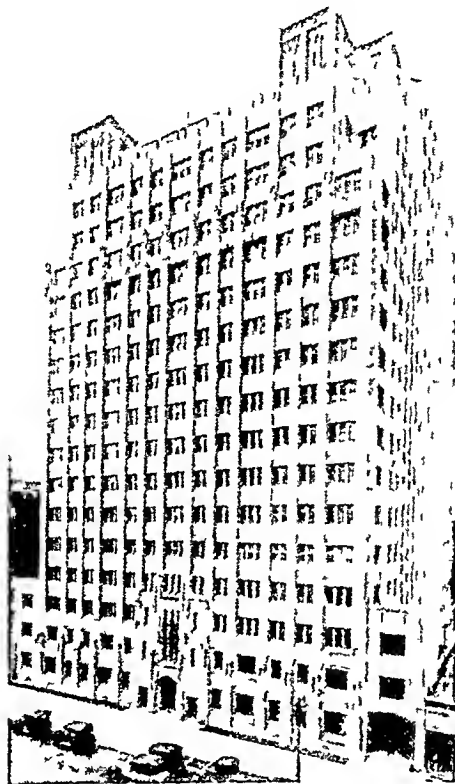
Jefferson's faculties, which weathered severe storms in the early days, have contained some of the most distinguished Philadelphia physicians of national reputation—such men, for instance, as George McClellan, already mentioned, John Eberle, Daniel Drake, Nathan R. Smith, Robley Dunglison, Joseph Pancoast, J. K. Mitchell, Thomas D. Mutter, Charles D. Meigs, Franklin Bache, Samuel D. Gross, Samuel H. Dickson, Robert E. Rogers, the younger Gross, J. M. DaCosta, Roberts Bartholow, W. W. Keen, Hobart Amory Hare, and J. C. DaCosta. The College's history is a colorful one, and its achievements loom large in the history of the city's and the nation's medical life.

Hahnemann Medical College and Hospital. In 1845, homeopathy had practitioners (about 250 in number) in 22 states, but no institution where homeopathy was taught. Its doctrine, in fact, was promulgated under a cloud of disapproval by the medical profession, which culminated in resolutions passed, in 1847, by the newly formed American Medical Association, tending to stigmatize it as irregular. It was in an attempt to gain legal recognition for the system that the Homeopathic Medical College of Pennsylvania, the oldest of its kind in the world, was founded in 1848. In 1869 this college was consolidated with the Hahnemann Medical College of Philadelphia under the corporate name of the Hahnemann Medical College of Philadelphia, and in 1885 the corporation of the Hahnemann Medical College and Hospital of Philadelphia was brought by merger into existence and located at its present site.

With admirable sincerity of purpose the College has pursued its course, constantly strengthening its base and widening its curriculum in line with the developments in the fields of medicine. Its requirements today include two years of college work as a minimum, preference being given those applicants with more preparation. The Medical School offers a standard four years' course, and confers upon its graduates, by provision of its state charter, two degrees, those of Doctor of Medicine and Doctor of Homeopathic Medicine. Special attention is given, of course, to the Department of Materia Medica and Therapeutics and to the principles of Hahnemann, Hering, Dunham, and other noted men in the field, but the prime object of the school is to give a broad and thorough medical education.

The College building contains lecture rooms, a large library and museum,

laboratories, rooms for operative surgery and practical obstetrics, the administrative and faculty offices and reading rooms. The College Library may be divided into two departments. One contains about 15,000 volumes and is especially of historical interest. Here are found Dr. Hering's notable



HAHNEMANN MEDICAL COLLEGE AND HOSPITAL. (Broad above Race Street)

collection of the writings of Paracelsus, Dr. A. R. Thomas' collection of very old and rare anatomical books, all of Hahnemann's works in the original and the most complete library of homeopathic literature in existence. The other constitutes a valuable working library and reading room for students and contains a file of the principal medical and scientific journals. Investigation in medical literature is considered an essential part of the college course.

The new Hahnemann Hospital, 20 floors in height, was opened in 1928 and has a total capacity of 700 beds, 370 of which are public. Over 12,000 bed patients are treated in a year, and during the past year 120,000 visits were made to the out-patient department. The Hospital is equipped with electrocardiographic, fluoroscopic, basal metabolism and clinical laboratories. The arrangements are such that the operating units are coordinated on the same floor with the roentgenological department, the clinical and pathological laboratories of the Hospital being on the floor directly below. As with

the other schools and hospitals which we have mentioned, the faculty of the School and the staff of the Hospital are one, and the clinical material presented by the Hospital is directly available for teaching purposes and is used constantly

The tendency of the day in this country is unquestionably toward greater uniformity in medical instruction, and to the advance along this line Hahnemann College has devoted itself with obvious success

Woman's Medical College of Pennsylvania The position of women in American medicine would probably be as uncomfortably anomalous today as it was in the early years of our national life, had there not come quietly into existence in 1850, in Philadelphia, an institution quaintly called, in the terminology of the day, the Female Medical College of Pennsylvania This was the first college in the world regularly organized for the medical education of women, and it is still the only medical school in the United States exclusively for women



WOMAN'S MEDICAL COLLEGE (Henry Avenue and Abbotsford Road)

The opening session of the College found 40 students enrolled for instruction by a faculty of six, all men The first class graduated numbered eight, of whom one, Dr Ann Preston, was soon elected to the Chair of Physiology and Hygiene, the first woman to have a place on the faculty Today over two-thirds, about 70, of the faculty are women

It is to be expected that the problem of adequate clinical instruction would be a difficult one for the pioneers to overcome, and such indeed it was In 1860 we find the first official reference to the founding of the Woman's Hospital of Philadelphia A lack of foresight in the acquisition of its charter, however, led to a situation in which the College and the Hospital came under the management of dual groups, which hindered the use of the Hospital for clinical teaching Fortunately, other clinical opportunities were opening up On January 2, 1869, the distinguished Alfred Stille prefaced his lectures in the amphitheater of the Philadelphia Hospital with these words

"Ladies and Gentlemen I have pleasure in meeting you today It is the first time in my medical experience that I have had the opportunity of addressing women among the audience of my pupils We are sometimes shocked at what is novel, simply because it gives us an unaccustomed impression, but in the present instance I must say that, so far as I am personally concerned, I not only have no objection to seeing ladies among a medical audience, but, on the other hand, I welcome them "

In 1869, likewise, the Board of Managers of the Pennsylvania Hospital came nobly to the rescue with an invitation to the women students to attend the clinical lectures at that institution On November 6 of that year about 30 women students accepted the invitation, but presumably somewhat to their chagrin The novelty was not only a shock to the male students of the Pennsylvania Hospital, but it was received with conduct on their part which quickly made of the incident a *cause celebre* The way of the pioneer, which is, in a sense, that of the transgressor, was ever hard

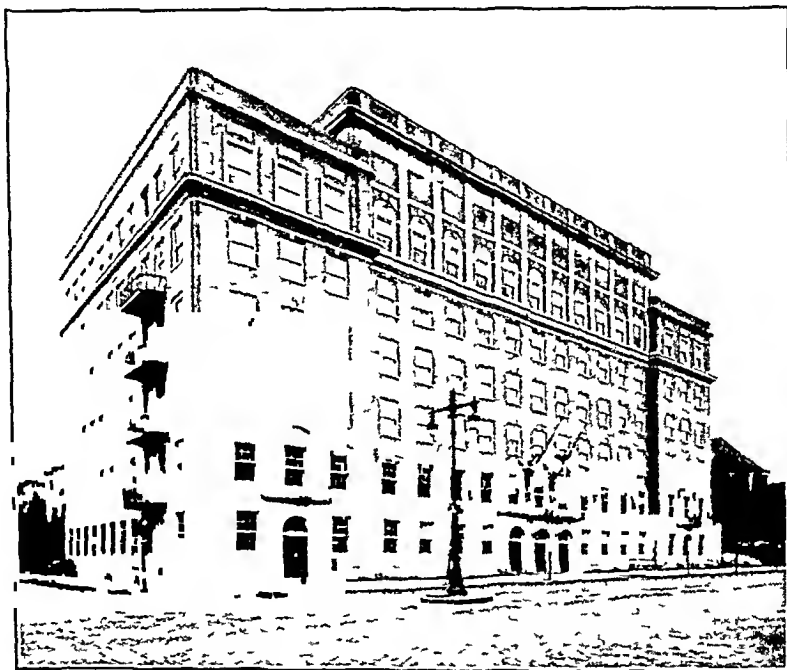
The site and buildings of the present College and Hospital, opened in 1930 and occupying approximately 10 acres, present the former Female College of Pennsylvania, under its present title, as one of Philadelphia's distinguished medical institutions The Hospital, containing 152 beds and 21 bassinets, is conducted by the Corporation under the professional direction of the faculty A fully equipped heart clinic was opened in 1932 and a bronchoscopic clinic in 1933 to 1934 An out-patient clinic is conducted at Barton Dispensary, 1309 North Twenty-Second Street, as well as at the Hospital The students enjoy many of the extramural privileges, such as the use of the Libraries of the College of Physicians and the Academy of Natural Sciences, and of various clinics, accorded their male colleagues If the millennium has not yet been attained, that is a circumstance of which we are all, men as well as women, in one way or another the victims Certainly, the work of the Woman's Medical College of Pennsylvania has contributed not a little toward defining the road forward

Temple University School of Medicine The Medical Department of Temple University was opened in 1901 It is, therefore, the youngest of Philadelphia's five recognized medical schools No one, however, with even a bowing acquaintance with the country's medical schools will be deceived by that fact Its status today as one of our major schools of medicine is uncontested This position it has achieved in comparatively few years, through its success in drawing to it a distinguished faculty and in furnishing them and their students with the most modern equipment for research and instruction Its success in attracting medical students may be gauged by the fact that, though the first-year class is limited to 100, in 1933 nearly 2000 applicants were considered by the Committee on Admissions

If the annals of this school are as yet too brief to provide a historian's field-day, it should at least be pointed out that the Temple University School of Medicine was the first coeducational medical school to be established in

Pennsylvania Its third graduating class, in fact, included two women Thus far at least had we traveled since the embattled days of '69

The present building occupied by the School was opened in 1930 It is situated on Broad and Ontario Streets, directly opposite the University's Hospital Dispensaries and administrative offices share with the library the first and second floors The various departments are housed in the third to sixth floors, while the seventh contains medical and research rooms and storage facilities for mammals, rodents, etc



TEMPLE UNIVERSITY SCHOOL OF MEDICINE (Broad and Ontario Streets)

The Temple University Hospital, where most of the clinical teaching is done, is directly under the control of the faculty It ranks with the larger institutions of its kind in the city in facilities and equipment, having a bed capacity of 469 which affords abundant material for every branch of clinical instruction A laboratory building on the hospital grounds provides a well equipped clinical laboratory, an autopsy room, private laboratories for original research and rooms for teaching purposes

Temple University itself, founded in 1884 by Russell H. Conwell, celebrated the past year its fiftieth anniversary The seal of the University bears the motto *Perseverantia vincit* As one looks at the achievements of its medical school in so short a period, one is almost tempted to believe that perseverance, soon or late, if the object be a fair one, does win

Philadelphia College of Pharmacy and Science It would certainly not be fitting to close this brief survey of Philadelphia medical schools without

recalling to the visitor's attention the fact that the Philadelphia College of Pharmacy and Science, at Forty-Third and Kingsessing Avenue, today one of the leading institutions of its kind in the country, was also the first college of pharmacy in the new world. The history of this college founded in 1821, in Carpenter's Hall, seat of the Provincial Assembly and of the first general Congress of the Colonies, covers practically the history of pharmaceutical education in this country. Its founding by 68 druggists and apothecaries bent upon education by the masters of their craft, indicates once more the early and deep devotion of Philadelphia's medical groups to the highest development of their science. And it is by way of illustrating the high quality of instruction which has always been maintained in the College that we recall as members of its faculties George B. Wood, Joseph Carson, Franklin Bache (great-grandson of Benjamin Franklin), Robert Bridges, William Proctor, John M. M. Maisch, Samuel P. Sadtler, and Joseph P. Remington.

Hospitals The hospitals which are directly connected with the various schools of medicine have already been briefly mentioned. We may be forgiven under the circumstances if from the many others we select for a brief introduction those which will be the most intimately involved in the forthcoming meetings.

The Pennsylvania Hospital To those who have the fortune to see medicine in its historical perspective, the Pennsylvania Hospital is perhaps more than any other medical institution in the country a rich source of pleasure. One of the largest and most important hospitals in the city today, it yet retains both in its exterior and in its interior much that is evocative of its long and notable past. It is, in fact, the oldest hospital in the United States which was intended wholly for the sick and wounded and which has continued on its ancient site and maintained its original name. The accompanying lithographic illustrations by Philadelphia's celebrated son, the late Joseph Pennell, speak more directly of the continuing beauty and charm of the place than any words which we might use. The famous double staircase is pictured here but not the old clinical amphitheater, first of its kind in America, the library, the notable paintings (including Benjamin West's "Christ Healing the Sick"), or many other carefully preserved witnesses of a distinguished life.

The founding of this Hospital was predominantly the work of Benjamin Franklin and his close friend, the physician Thomas Bond. The latter is remembered today also as the originator of the Bond splint for the treatment of fractures of the forearm, and for the invention also of an instrument for extracting foreign bodies from the esophagus, thus inaugurating what seems to have become an old Philadelphia custom.

The roster of the Hospital has always contained the names of many of the city's leading physicians—the Bonds, Morgan, Shippen, Jones, Rush, Physick, James Parish, Otto, Ward, Pepper, Gerhard, Agnew, Packard, Ashhurst, Hart. This gratuitous service was instituted by the Hospital's

first physicians. It is estimated that the services performed by the Staff today are worth over \$400,000 a year.

The divisions of the Pennsylvania Hospital today are the Department for the Sick and Injured, the Department for Mental and Nervous Diseases, and the Institute of the Pennsylvania Hospital. The Philadelphia Dispensary, founded in 1786, is now also carried on as part of the "Out-Patient Department of the Pennsylvania Hospital and Philadelphia Dispensary."



PENNSYLVANIA HOSPITAL FROM THE GROUNDS

The Pennell drawings of the Pennsylvania Hospital, which appeared originally in "Our Philadelphia" are reproduced through the courtesy of Mrs. Joseph Pennell and the J. B. Lippincott Company, of Philadelphia.

The Department for the Sick and Injured, at Eighth between Spruce and Pine Streets, occupies the site it first moved to in 1756. An interesting analysis of its service, as given in the Hospital's most recent Annual Report, indicates that during the year there was an application for either emergency or ward care every 14 minutes, a ward bed or a private room received a new patient every 84 minutes, the Out-Patient Department cared for a patient

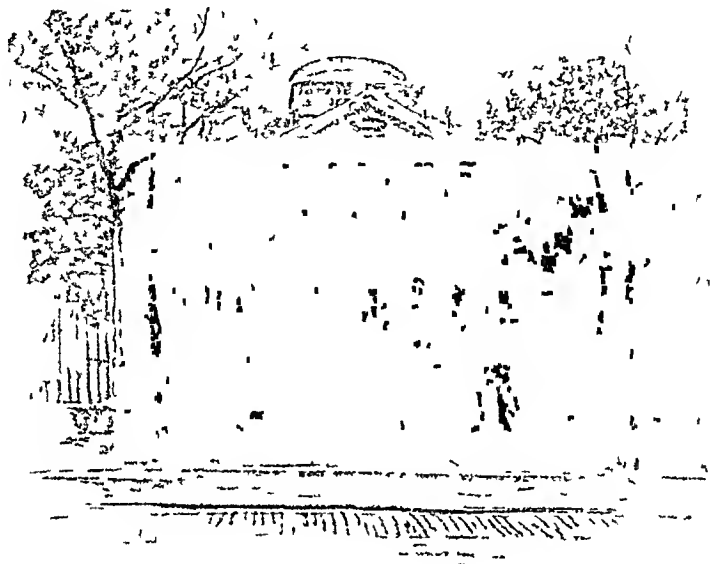
every three and two-fifths minutes, the police patrols brought a patient to the door every five hours and 22 minutes, a surgeon performed an operation every two hours and four minutes. No further words are needed to show that this Department of the Hospital, which, like the Jefferson College Hospital, is in the center of the city, fulfills the extraordinary demands made upon it as courageously as it did in the days when it was a new institution in a New World.



THE DOUBLE STAIRWAY OF THE PENNSYLVANIA HOSPITAL.

The Department for Mental and Nervous Diseases and the Institute are reminders that the Pennsylvania Hospital from its origin was the pioneer in the Colonies in the treatment of the mentally unstable not as criminals but as patients suffering with mental disease, subject to individual treatment and eventual return to reason. This department was moved to its site in West Philadelphia, at Forty-Fourth and Market Streets, in 1841, and its first Superintendent, Dr. T. S. Kirkbride, so impressed his personality upon the

institution that, for many years, it was familiarly known as "Kirkbride's." The treatment of its more than 200 patients is naturally on an individual basis, planned after a comprehensive study of the patient, and employs such methods, depending on the diagnosis, as fever, occupational and physiotherapy, the Aschner treatment, music, recreation, etc. It may be of interest that the latest published statistics show that 36 per cent of those committed in the last year were diagnosed as having manic-depressive psychoses, while cases which set into no definite mould of mental disease constituted another 21 per cent.



PENNSYLVANIA HOSPITAL FROM PINE STREET

The Institute, at Forty-Ninth and Market Streets, represents the Hospital's latest development in the line of treating mental conditions. The keynote of its work is that of prevention of mental and nervous illness. Here in quiet and comfortable surroundings the attempt is made to solve the emotional problems as much as possible by natural means under medical direction. Civic recognition of the work of the Institute was signalized in 1933 by the presentation of the Philadelphia Award to the Chief of Clinical Service and Medical Director of the Institute. The career of the Pennsylvania Hospital has been memorable in many ways, in none other perhaps so memorable as in its steady devotion to the understanding and healing of the mentally sick and injured.

Philadelphia General Hospital. The Philadelphia Almshouse was erected in 1731 or 1732. In 1835 it officially adopted the title "Philadelphia Hospital," which again gave way, in 1902, to the title it bears today, namely, "Philadelphia General Hospital."

The history of this institution from its earliest days as an alms- or

"bettering" house, receiving, in the older fashion, the poor, the sick, and the lunatic, to its position today as the largest hospital in the city and one of the largest in the country, forms one of the more remarkable chapters in the history of medicine in Philadelphia

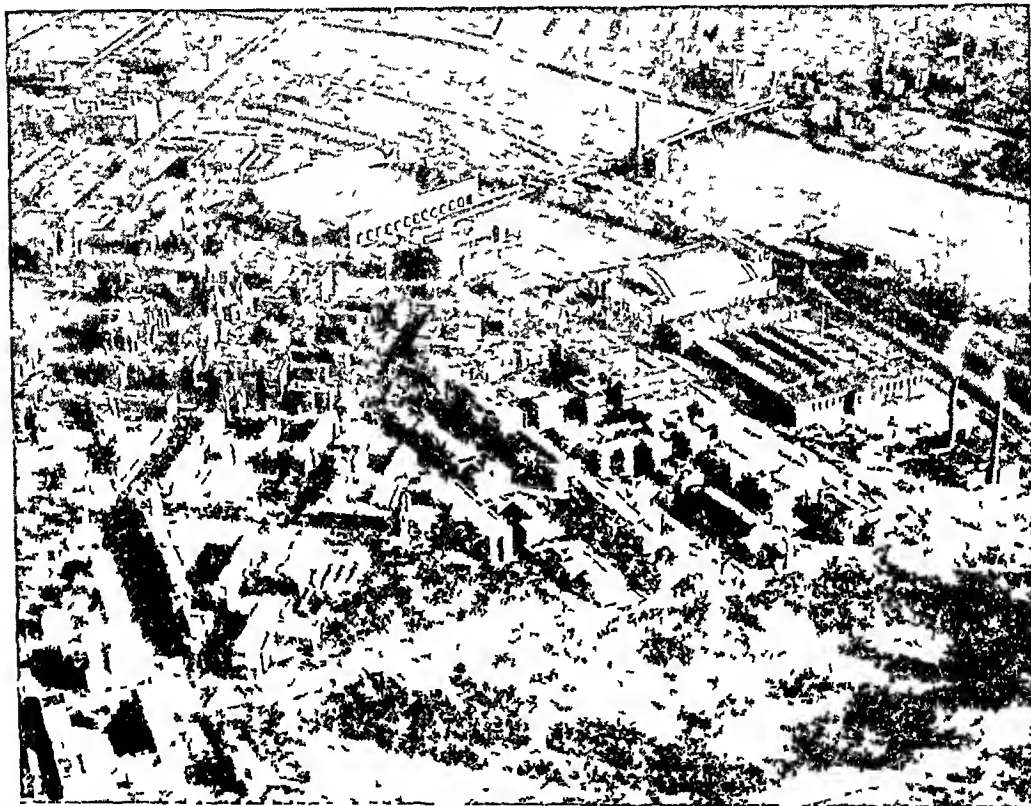


THE INSTITUTE OF THE PENNSYLVANIA HOSPITAL (Forty-Ninth and Market Streets)

Though the title "Philadelphia Hospital" was not adopted until 1835, there is ample evidence that a hospital department existed at the Almshouse from its early days. And the title adopted in 1835 was again curiously inconclusive in that the Almshouse and the Hospital continued to be located together at the present site of the Philadelphia General Hospital until 1920, when the Almshouse was removed to separate quarters away from the hospital grounds.

The earliest records of the Hospital, unfortunately not so well preserved as those of the Pennsylvania Hospital, show that the pre-Revolutionary attending physicians numbered many of the famous group so intimately connected with the founding and the early days of the Pennsylvania Hospital and the Medical School of the present University of Pennsylvania. Since those days the staff of the Hospital has included at one time or another Philip Syng Physick, Caspar Wistar, Benjamin Smith Barton, Nathaniel Chapman, T. C. James, Hugh Lenox Hodge, S. D. Gross, D. Hayes Agnew, William Osler (whose notable postmortem work was done here), S. Weir Mitchell, J. H. Musser, H. C. Wood, Louis A. Duhring, W. W. Gerhard (it was in this Hospital that he made his clinical observations on the differentiation of typhus from typhoid fever), DeForest Willard, and others of equal prominence.

When the Hospital moved, in 1834, to its present site and assumed officially the name "Philadelphia Hospital," it assumed unofficially the name "Blockley", from the township in which it was placed, and this was the name by which it was commonly known, to which it still occasionally answers today. In 1834 it was supposed to accommodate 400 sick, 200 more, if necessary, and was difficult of access from the medical schools. Today it has a capacity of about 2700 beds and has as its near neighbor the Medical School of the University of Pennsylvania.



AN AERIAL VIEW, SHOWING THE UNIVERSITY OF PENNSYLVANIA TODAY (LEFT), THE PHILADELPHIA GENERAL HOSPITAL (RIGHT CENTER), THE STADIUM, AND THE CIVIC AUDITORIUM

The greatest strides in the New Philadelphia General Hospital have been taken in the last 15 years. This period has seen the development of the out-patient clinics to which in the past year 44,642 visits were paid. Particularly noteworthy is the work being done in cardiology, in metabolism, in occupational diseases, in tuberculosis, in radiology, and in the neuropsychiatric, prenatal, and postnatal clinics. The Saturday morning clinics, for the general practitioners of the city, are a prominent feature of the Hospital's life today. Cases of special interest in the Hospital are drawn upon for material and some prominent physician, not necessarily of the staff, is invited to talk upon them.

This period has seen, also, the erection of a building for the adequate housing of the interns and resident physicians, and one for the care of the female tuberculous. The impressive proportions of the Philadelphia General Hospital today, an idea of which can be readily gained from the accompanying aerial view, and the notable work which it continues to do, are further tributes to the vigor and integrity of Philadelphia's medical men who have had occasionally in making this Hospital possible, severe political battles to wage in order to maintain adequate scientific independence and progress.

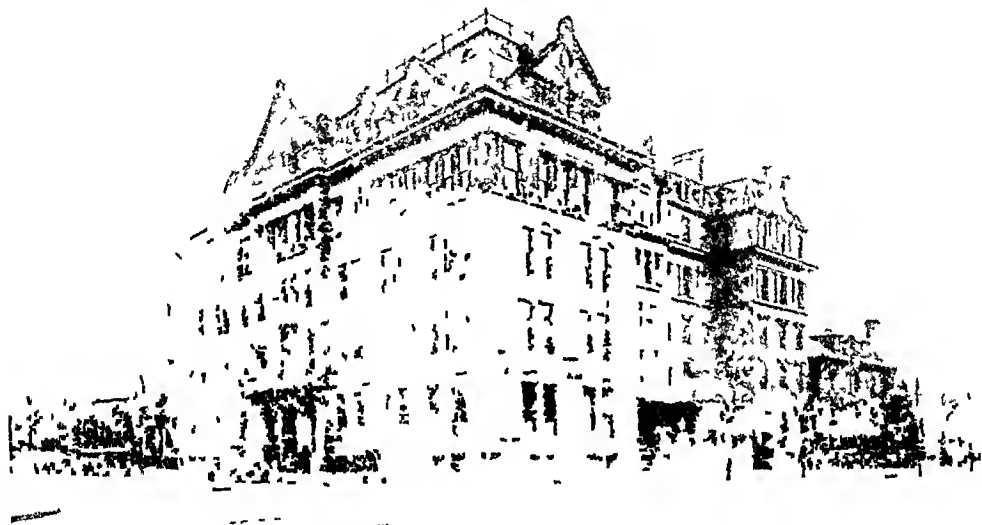


CHILDREN'S HOSPITAL (Bambridge Street entrance)

The Children's Hospital The Children's Hospital of Philadelphia, at Eighteenth and Bambridge Streets, in the past year opened another wing (Rush) of its projected final group. This well emphasizes the continuing growth of the country's oldest hospital designed exclusively for children, established in 1855, and the third such hospital in the world. The first home of the Hospital had accommodation for 12 patients, the present Hospital, opened in 1916, has a capacity of 156 beds.

The primary purpose of the Hospital was to care for children suffering from diseases which could not be properly treated in their homes. An interesting commentary on the changes of direction which the progress of medicine takes is the Hospital's Department for Prevention of Disease inaugurated in 1914 as an outgrowth of a previous Social Service Depart-

ment This Department, the first of its kind in any hospital in America and one which draws visitors from all over the world, treats annually both in their homes and in the clinics well over 100,000 patients This, in addition to an annual regular out-patient service of over 40,000 visits and an in-patient roll of approximately 3000 patients, is sufficient evidence of the remarkable service which this Hospital gives to the children of Philadelphia As a further development in the general field of Child Welfare, the Hospital established in 1923 a Child Guidance clinic This clinic was designed to examine and recommend the right management of problem children,



LANKENAU HOSPITAL (Girard and Corinthian Avenues)

truants, potential criminals, and other misfits It has under its guidance constantly over 800 of these children Philadelphia, once again, has proved itself a pioneer in the now accepted doctrine, proposed so early in our medical history by the Pennsylvania Hospital, that the physician can not exclude from his realm the unsound mind, no matter how sound the body

Lankenau Hospital The Lankenau Hospital, incorporated in 1860, opened for patients in 1866 as the German Hospital of the City of Philadelphia Its present name honors its second President, John D Lankenau, whose personal care and generosity are credited with being the chief agents through which it reached its present standing among the city's hospitals

Originally designed as a hospital in which the German people of Philadelphia might be treated by physicians and nurses who could speak their native tongue, the Hospital has inevitably come to serve a wider function Though the Hospital is excellently equipped for its annual in-patient service demand of about 4000 patients and an out-patient visit total of about 37,000, probably its chief interesting feature is its Research Institute This was built in 1925 by the late Rodman Wanamaker, at the cost of about half a

million dollars. The activities of the Clinical Laboratories of this Research Institute include in a year about 60,000 examinations of all types. A Division of Art and Photography records the completion of numerous drawings, photographs, and photomicrographs of patients, specimens, and apparatus, which are used for following the progress of patients, for teaching, and for illustrating contributions to medical literature. A filing system allows quick collection of previously completed illustrations of a large variety of subjects. The Out-Patient Departments, the Diagnostic Clinic, and the Maternity Department have profited particularly from the work of the Institute in the ability that it provides to reconstruct early conditions



PRESBYTERIAN HOSPITAL (North Thirty-Ninth Street)

The Research Division of the Institute, as is now generally known, has concerned itself with the problem of the chemistry of cell growth, and its researches in the subject of sulphur metabolism have directed attention from many quarters to the work of the Institute and the Hospital of which it is a part.

Presbyterian Hospital The Presbyterian Hospital, incorporated in 1871 and opened the following year, was a happy product of the reunion, in 1869, of the two branches of the Presbyterian Church.

This Hospital, which never has had any restrictions as to race, creed, or color, has a consulting and major staff of about 170, and provides beds for

425 patients The Out-Patient Department, with an annual visit-total of about 63,000, offers clinics in allergy, diseases of the heart, diabetes, thyroid and other conditions A Child Health Clinic follows the Department for Prevention of Disease of the Children's Hospital, in emphasizing the modern doctrine of prevention

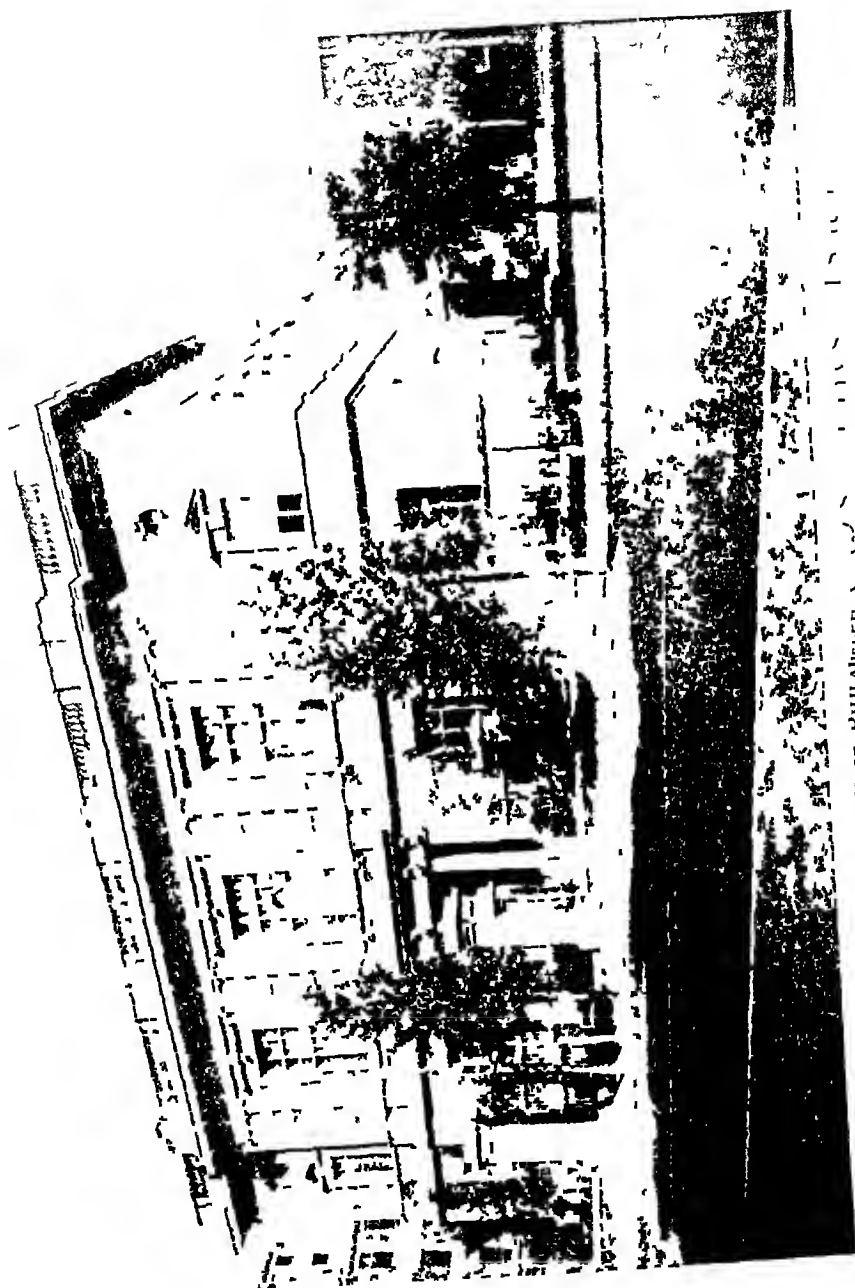
The physicians and interns, as in most hospitals, hold weekly clinical conferences in the laboratory for the discussion of unusual pathological conditions which arise in the routine of observation in the Hospital, and papers and other presentations are delivered at monthly scientific meetings Recently a research committee has been instituted with a view to extending the general importance of the work done in the Hospital

In general, cooperation between the Hospitals and the Medical Schools, which we have hinted at in speaking of the Graduate School of Medicine's "Pennsylvania Plan," is engaged in widely, and there can be little doubt that its ultimate effect is an advantageous one for all concerned

It is to be expected that a city so rich in medical institutions should be rich alike in medical societies About 50 of these advertise their meetings in the Weekly Roster published by the Philadelphia County Medical Society, and these do not constitute the entire list, of course Of these, two must be mentioned The largest in the city is the Philadelphia County Medical Society, at Twenty-First and Spruce Streets Organized in 1849 under the presidency of Dr Samuel Jackson, it has been from the beginning an extraordinarily active and effective medical police in the interests of the public welfare Of late years it has become increasingly active in stimulating the interest of the younger physicians, the interns and medical students, by series of postgraduate seminars and round table discussions held in its building The Weekly Roster which it publishes is an invaluable guide to the activities of the city's medical societies

The oldest existing medical society in Philadelphia, and the most famous, is, of course, the College of Physicians, organized in 1787 Its present splendid home, which was built for it and to which it moved in 1909, houses one of the finest medical libraries in the world, both in size and in quality Its collections of medical incunabula and other medical books of the greatest rarity are known in Europe as well as in this country Over 200 of the incunabula have already been photostated by the Library's photostatic machine and are accessible to scholars in the reading room * These collections and one of the most comprehensive files of medical periodicals in the country have resulted in making the College a court of first resource for those working in medical literature The College holds monthly scientific meetings, except during the summer, often with distinguished guest speakers, and its Fellows have organized five Sections which likewise hold monthly meetings in the lecture halls of the College, which are used also by other medical societies in the city The College, thus, is open six full days and many eve-

* A special exhibit of some of the rarest items has been arranged for the American College of Physicians and, likewise, arrangements have been made to introduce its members to the Mütter Museum and other treasures in the College building



THE COLLEGE OF PHYSICIANS OF PHILADELPHIA

nings in the week, carrying on that "diffusion of medical knowledge" proposed as among its objects by one of its distinguished founders, Benjamin Rush

Philadelphia's medical activities today include, further, the publication of 19 medical journals. Philadelphia is the home of five of the largest medical publishing houses in the country. Here are the headquarters of the American College of Physicians. Philadelphia today teaches medicine, practices medicine, thinks in terms of medical progress with the singular devotion which it inherits and passes on year by year. It is, in a spiritual sense at least, the medical center of America.

EDITORIAL

THE CERTIFICATION OF INTERNISTS AND THE PROPOSED EXAMINATIONS FOR FELLOWSHIP IN THE COLLEGE

THERE has been a well defined movement in American medicine towards the establishment of more definite criteria for the title of specialist. The ophthalmologists, the pediatricians, the neurologists and psychiatrists have either established special examining boards for certifying specialists in their respective fields or are in process of setting up machinery for so doing. The leadership in this movement has been taken by the American Medical Association, and its participation in the certifying process has recently been defined as follows:

ESSENTIALS FOR EXAMINING BOARDS IN SPECIALTIES

By the Council on Medical Education and Hospitals of the American Medical Association, Chicago

I ORGANIZATION

- 1 A special examining board to be approved by the Council should represent a well recognized and distinct specialty of medicine
- 2 It should be composed of representatives of the national organizations of that specialty including the related section of the American Medical Association
- 3 It should be incorporated
- 4 A special board should
 - (a) Determine whether candidates have received adequate preparation as defined by the board
 - (b) Provide a comprehensive test of the ability and fitness of such candidates
 - (c) Certify to the competence of those physicians who have satisfied the requirements of the board

II DEFINITION OF SPECIAL FIELDS

The following branches of medicine at present are recognized as suitable fields for the certification of specialists:

- | | |
|-----------------------------|-------------------------------|
| 1 Internal Medicine | 7 Dermatology and Syphilology |
| 2 Surgery | 8 Neurology and Psychiatry |
| 3 Pediatrics | 9 Urology |
| 4 Obstetrics and Gynecology | 10 Orthopedic Surgery |
| 5 Ophthalmology | 11 Radiology |
| 6 Otolaryngology | 12 Pathology |

In the Milwaukee Session of the House of Delegates a resolution was adopted which read as follows:

"Resolved, That the Council on Medical Education and Hospitals is hereby authorized to express its approval of such special examining boards as conform to the standards of administration formulated by the Council, and be it further

"Resolved, That the Board of Trustees of the American Medical Association be urged to use the machinery of the American Medical Association including the pub-

lication of its Directory, in furthering the work of such examining boards as may be accredited by the Council "

It is apparent, therefore, that the way is open for the American College of Physicians as the largest and most representative body of internists in this country to ally itself with the Section on the Practice of Medicine of the American Medical Association in setting up an examining board for the certification of specialists in internal medicine

The decision of the College as to whether it should assume this responsibility is undoubtedly an important one both to the future of the College and to the success of the movement towards certification of specialists. The question deserves examination in some detail

In the first place one may well ask what is the purpose of certifying specialists. The only valid answer would seem to be that such certification would constitute a natural and valuable extension of the laws of licensure of physicians. These laws are primarily for the purpose of ensuring to the public that those men who establish themselves in the community as practitioners of medicine have had adequate training to fit them for the responsibility they have assumed. It is inevitable that the public should some day demand that those physicians who assume the rôle of specialists in some field of medicine, with the definite further responsibilities that such a rôle entails, should likewise be forced to demonstrate adequate training and experience. Such a public demand has not yet become vocal but it would be justified. That this movement towards certification of specialists arises in the medical profession itself is excellent evidence that the members of that profession in this country are able to govern and to discipline themselves. The interest of all physicians in this attempt at self government may well be stimulated by the evidence available in another field of medical activity, medical economics, that when the profession fails to regulate its affairs wisely we are apt to suffer from laymen's attempts to rule us through unintelligent and unsympathetic laws

If the medical profession of this country is to certificate its specialists in the near future, rather than await the day when legal licensure of specialists by State Boards will be forced upon us, it is evident that it is only by agreement of all in a common procedure, by just and impartial administration of the tests applied, and by education of the public in the meaning and value of the certification that success will be achieved. It seems apparent that the American Medical Association must be the coordinating body through which the work of the various Examining Boards is controlled and the results made public. Attempts of various associations, societies, academies or colleges in the separate specialties, no matter how powerful, to set up their own examining boards and claim public recognition for their members could end only in confusion and discredit to the profession. The question as to whether to take an active part in this movement under the leadership of the American Medical Association is one to be considered by each national organization in the special fields, but no plan for maintaining a competing

certifying board could be justified. On the other hand when a dominant national organization joins hands with the American Medical Association in this movement it might justly demand a controlling voice in determining the criteria for certification in its special field.

The question of the participation of the American College of Physicians in the certification of internists bears interesting relationships to the problems connected with the requirements for Fellowship. It so happens that there has been active discussion for some time among the Regents of the College, as may be seen in the minutes of their last meeting in Philadelphia, as to the advisability of requiring some form of examination for admission to Fellowship in the College. It is felt that the present methods of determining eligibility do not afford to the Committee on Credentials adequate information on which to base their decision, and a variety of more formal tests has been proposed. The opinion of the regents committee, appointed to consider this subject, has so far been divided both as to the advisability and the feasibility of instituting a system of practical and written examinations, which the candidate from the ranks of the Associates would be required to pass before the Fellowship was conferred. There has been discussion also as to the value to be assigned to postgraduate work, to original investigations, and to publications.

If the College should decide to play an active role in conjunction with the Section on the Practice of Medicine in certifying internists, no doubt such certification as an internist would become one of the prerequisites to application for Fellowship. Since all physicians desiring to be known as internists would be taking the examination of the certifying Board of Examiners the College would not be requiring an unusual test which might deter some desirable men from applying. It would also be in the more advantageous position of not receiving applications from those who had failed the examination of the certifying Board, rather than of being forced to reject a candidate because after applying he had been unsuccessful in passing the tests given by the College. The College would of course reserve its privilege of selecting from applicants who had passed the certifying examination only those who satisfied all other requirements for Fellowship.

The further requirements which should be met before a certified internist became eligible for Fellowship in the College would no doubt vary in the course of the years. The standard of requirements would progressively grow higher so that the title of Fellow would always mean not only adequate training and experience in internal medicine but especial distinction in professional ability, leadership and character. It might justly be expected that the young physician who adopted internal medicine as his career would be guided in his training by the requirements necessary to reach two successive goals, first the passing of his examination before the certifying Board and second his election as a Fellow of the American College of Physicians. In the interim years of his training he should find, as Associate member of the College, a valuable stimulus in the Annual Clinical Sessions. Perhaps in

time the Regents, Governors and Senior Fellows in each state may come to be the natural advisors and aids to the younger Associates who are seeking opportunities for further training in internal medicine. The College might well feel that no finer program could be adopted as its chief aim than to stimulate and assist young physicians in the study and practice of internal medicine, to ensure a fair and thorough method of their certification as internists, and to reward their further accomplishments by the bestowal of its Fellowship.

Desirable as such a program seems to be, it must be realized that the road to its establishment is beset with many practical difficulties.

The question of certification after examination must be so managed that the interests of those men already well established in practice must be safeguarded as must indeed the rights of those men already elected to Fellowship in the College. The character of the required training in internal medicine and the nature of the comprehensive examination for certification must be such as will not bar the man who is unable to finance many years of pure postgraduate study, and also such as will not permit a semblance of sound postgraduate study to pass for the reality. There is likely to be serious difficulty also in obtaining the proper personnel and facilities necessary for examining annually, or semi-annually the very large number of candidates who will apply.

It is obvious that before the American College of Physicians decides to take part in this movement it will be necessary to find a solution to these and many other practical difficulties. It is felt that from the Fellows and Associates of the College many valuable suggestions might come, as to the advisability of the undertaking, as to proper criteria for awarding certificates and as to feasible plans for the conduct of the examination. The advice of all members of the College will be welcomed. Communications addressed to the Editor will be placed before the Committee on Examinations. The whole question will be among the most important of those coming up for discussion before the governing bodies of the College at the coming sessions in Philadelphia.

REVIEWS

Definite Diagnosis in General Practise By W L KITCHENS, M D 445 pages,
18×26 cm W B Saunders Company, Philadelphia 1934 Price, \$10 00

It is quite difficult to form an opinion about this very unusual book without a trial in practise. It is purely an index, with no text except eight pages of preface and instructions in the use of the volume. Consequently, its usefulness is almost as difficult to estimate as that of a card index file.

The volume is divided into two parts, the first of which lists, at the head of each page, a symptom of diagnostic importance. Under each symptom are listed those diseases in which the symptom occurs with a page number referring to the second section of the book. Altogether, 506 symptoms are listed. A sub-index, heading this section, serves as a guide and cross-index.

The second section is made up of 407 pages, each devoted to the symptomatology of a disease. Each symptom listed is numbered, the number referring to a page in the first section headed by that particular symptom.

Thus, page 140, in part one, is headed "Dyspnea." Listed here are 65 diseases or pathological states in which dyspnea may occur, with page numbers indicating the section in part two listing the symptomatology of each of these diseases. Four hundred and seven diseases are listed in all.

The author states in his introduction that this book cannot take the place of a text. This is, of course, quite true. Descriptions of neither diseases nor symptoms are given, and to pass judgment on a patient without confirming the book's suggestions appears difficult or impossible. No attempt is made to classify symptoms as to their major or minor importance in any disease, nor to indicate whether symptoms are due to the disease itself or a complication.

Certain striking omissions are noted. Cyanosis is not mentioned as occurring in pulmonary embolism or pulmonary edema. Fever, pericarditis, and leukocytosis are not listed under coronary thrombosis. The author has made some provision for these and other omissions, as there is ample space on each page for the physician's own list of additional symptoms and diseases.

This book should be of use in differential diagnosis, and as an easily available symptom list in teaching. It is doubtful, however, if it will make diagnosis as simple, easy, and definite as stated on the jacket.

T N C

Synopsis of Genito-Urinary Diseases By AUSTIN I DODSON, M D 275 pages
C V Mosby Co, St Louis 1934 Price, \$3 00

This small synopsis of 265 pages of text is somewhat of a departure from the stereotyped textbooks on genito-urinary diseases in that it does not take up the genito-urinary system in the order of its anatomical arrangement but rather emphasizes the attack of various diseases on the structures in proportion to their common occurrence. It is illustrated by eight photographs and 103 descriptive illustrations, the author having availed himself of the use of some of the best drawings of other books on genito-urinary diseases.

Chapter 2 is distinctive in that it shows drawings and photographs of the common instruments and procedures used in diagnosing and treating infections in the lower urinary tract. Although in this small book infections of necessity have been dealt with in a brief manner, there are over two pages devoted to the treatment of gonorrheal urethritis. This is excellent because this book will be read by many general practitioners and here is an outline to be observed in the management of this type of case.

In Chapter 10 the newer views of stone formation are sketched and the significance of associated infection is explained. The author says in the chapter on Prostatism that "The excellent results obtained in prostatic surgery are due chiefly to the careful preoperative treatment"

J H 1

What We Are and Why By LAURINCE H MAYERS, M D, and ARTHUR D WITTON
340 pages, 14.5 × 21 cm Dodd, Mead and Company, Inc, New York 1933
Price, \$3.00

The title and subtitle of this interesting little book indicate its general trend and the contents confirm the indication that there is, in the authors' opinion, only one important determinant of human conduct or of dispositional traits.

The authors' main thesis is that the infectious diseases of childhood, measles, whooping cough, scarlet fever, diphtheria and especially mumps, are lamentably frequent, are usually neglected and often exert a harmful effect on the endocrine glands, with the result that the unfortunate victim must go through life handicapped by physical disabilities, by personality defects, or by both. The authors state in the preface that it is their hope that their illustrative cases may have some influence in warding off from gland victims the opprobrium which they so often receive.

The book, designed for the layman, is attractively written with a breezy, easily readable style. The case reports are dramatically interesting instead of being dull and tedious and they are illustrated by excellent photographs. Nevertheless, a conservative reviewer cannot recommend, except for its entertaining qualities, a book so untrammelled by scientific rules. Many of its most entertaining features are based upon analogy or fancy, indeed, on page 217, the authors poke gentle fun at physiologists, pathologists and other punctilious scientists who are bound by hard rules of scientific evidence, and again on page 226, they say, "None of these statements coincides with the scientific observations of the physiologists."

Lacking these handicaps the book abounds in entertaining and sweeping statements, as for example, on page 232, "Naturally the experiments have been extensive and naturally there is variation in results and opinions but there is none in the belief that in the pituitary is found the center and stimulus of activity, both physical and mental." Again on page 195, "It is not our purpose to account for flagpole sitting or to try to classify it as a form of self-expression. It is mentioned only as an example of emotional eccentricity, founded in exhibitionism, which is infantilism, which is a result of glandular derangement."

The book presents cleverly and attractively the viewpoints of psychologists who have given endocrinology a joyous and enthusiastic welcome.

T P S

Arteriosclerosis, A Survey of the Problem Edited by EDMUND V COWDRY xvii
+ 617 pages, 16.5 × 24 cm The Macmillan Co, New York Price, \$5.00

This volume presents a survey of the problem of arteriosclerosis. There are, including an Introduction by Ludwig Aschoff and a Summary by Alfred E Cohn, twenty-three contributors. The book has twenty-one chapters, in each of which the problem is approached from a different aspect. It is attacked from the historic, the physiologic, the chemic, the statistical, the pathologic, the etiologic, the clinical and other points of view. It is stated that the contributors have had three objects clearly in mind: "To determine the data concerning arteriosclerosis which can be regarded as established and their relation to one another, to discover and definitely formulate the principal problems awaiting solution, and to suggest the best means of attacking them." The reviewer considers that this volume is a valuable step in attaining such objectives. It is an exhaustive compendium of present knowledge relating to the

subject, and many suggestions are offered for the furtherance of that knowledge. The various sections are furthermore surprisingly uniformly well written and interesting. There are included extensive references to the literature extant. The clinician will find this volume an excellent summary of present day knowledge of arteriosclerosis.

W S L, JR

Hygiene for Freshmen By ALFRED WORCESTER, A M, M D, Sc D, Henry K. Oliver
Professor of Hygiene, Harvard University viii + 154 pages, 15 X 25 cm
Charles C Thomas, Baltimore 1934 Price, \$1.50

This is a brief and rather informal textbook used in the Freshman course in Hygiene at Harvard University. The course, as described, is a weekly series of lectures throughout the first semester, and the textbook is apparently a summary of the lectures as they are delivered to the students.

In order to overcome the lack of a preliminary course in biology, the author has presented a clear and interesting summary of the essential biological and physiological processes, and correlated them with everyday life and habits. Following this plan, the student is introduced, by short but comprehensive chapters, to biology and embryology, the circulation, glands of internal and external secretion, nutrition, digestion, muscular physiology and the nervous system.

The chapter on mental hygiene should be especially valuable to the college freshman, discussing as it does, the new responsibilities, problems and conflicts that beset the freshman student, and the danger signals that indicate the necessity of psychiatric help. The discussion of reproduction and physiology of the sex organs is sound and well written, and should be of help to the late adolescent entering a difficult period of life. The course closes with chapters on prevention of disease and immunity.

In general this book gives one the opinion that the average student, and especially the student in medical school, should be benefited by becoming acquainted with it, and by application of its principles.

T N C

PROGRAM
NINETEENTH ANNUAL CLINICAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
PHILADELPHIA, PA

April 29-May 3, 1935

GENERAL SESSIONS

Jonathan C. Meakins, President

PHILADELPHIA COMMITTEES

Alfred Stengel, General Chairman

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Alfred Stengel, Chairman

T. Grier Miller
Ross V. Patterson
O. H. Perry Pepper

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William D. Stroud
Pennsylvania Hospital
Edward Weiss
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G. Harlan Wells
Hahnemann Hospital
Edward B. Krumbhaar
University of Pennsylvania School
of Medicine

Charles C. Wolferth
Hospital of the University of Pennsylvania

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COMMITTEE ON ENTERTAINMENT OF VISITING WOMEN

Mrs George Morris Piersol, Chairman

Mrs E J G Beardsley

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Mrs O H Perry Pepper

Mrs Truman G Schnabel

Mrs Alfred Stengel

Mrs William D Stroud

Mrs Robert G Torrey

Mrs H B Wilmer

Mrs Charles C Wolferth

DIRECTORY

General Headquarters

Hotel Headquarters

General Registration

Board of Regents

Board of Governors

Executive Secretary's Office

Publicity, Press Room

Technical Exhibits

General Scientific Sessions

Morning Lectures

Convocation

Annual Banquet

Ladies Registration and Headquarters

Municipal Auditorium, 34th St below Spruce

The Benjamin Franklin Hotel, 9th & Chestnut Sts

Exhibition Floor, Municipal Auditorium

Room 200, Lobby, Municipal Auditorium

Room 200, Lobby, Municipal Auditorium

Room 103, Exhibition Floor, Municipal Auditorium

Exhibition Floor, Municipal Auditorium

Exhibition Floor, Municipal Auditorium

Arena, Municipal Auditorium

Exhibition Floor, Municipal Auditorium

Ballroom, Benjamin Franklin Hotel

Ballroom, Benjamin Franklin Hotel

Franklin Room, Mezzanine Floor,

Benjamin Franklin Hotel

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1935 (dues, if not paid previously, may be paid at the Registration Bureau)
- (b) All newly elected members
- (c) Members of the College of Physicians of Philadelphia and of the Philadelphia County Medical Society, without registration fee, upon presentation of their 1935 membership cards, exhibits, general sessions and for the special morning lectures

- (d) Senior medical students pursuing courses at the University of Pennsylvania School of Medicine, Jefferson Medical College of Philadelphia, Woman's Medical College of Pennsylvania, Hahnemann Medical School and Hospital, and Temple University School of Medicine, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions, exhibits, general sessions and for the special morning lectures
- (e) House Officers of the hospitals participating in the program, upon presentation of proper identification, exhibits, general sessions and for the special morning lectures
- (f) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials
- (g) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of \$12 00, and shall be entitled to one year's subscription to the "Annals of Internal Medicine" (in which the proceedings will be published), included within such fee

REGISTRATION BUREAU—Temporary Registration Bureau will be open on the mezzanine floor of the Benjamin Franklin Hotel on Sunday afternoon and evening, April 28. The permanent Registration Bureau will be located at the entrance to the Exhibition Room of the Municipal Auditorium. Hours 8 30 A M to 6 00 P M, daily, April 29–May 3.

REGISTRATION BLANKS FOR SPECIAL MORNING LECTURES AND FOR ALL CLINICS AND DEMONSTRATIONS will be sent with the formal program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

CHANGES OF ADDRESS, errors in names, etc., should be reported at the Registration Bureau.

THE CASHIER'S DESK at the Registration Bureau will receive payment of dues still delinquent, and accept orders for Banquet tickets, the College Key, the framed Fellowship Pledge, the Fellowship Certificate Frame and subscriptions to the "Annals of Internal Medicine."

BULLETIN BOARD FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau in the Municipal Auditorium.

TRANSPORTATION—Round trip tickets may be procured on the basis of one and one-third of the current one-way first class fares, with minimum excursion fare of \$1 00 for the round trip, upon presentation of identification certificates to be procured from the Executive Secretary of the American College of Physicians. The reduced fares apply for physicians and dependent members of their families.

Members are privileged to make the going journey by one route, and return by another route. The fare for children of five and under twelve years of age will be one-half of the round trip fare for adults, children under five years of age free when accompanied by parents or guardian. Stop-overs will be allowed at all stations within final limit on either going or return trip, or both, upon application to conductors.

Before purchasing tickets, members must secure from the Executive Secretary an Identification Certificate, to entitle them to the reduced fares.

In general, tickets will be sold from April 17 to May 1, depending upon the relative distance from Philadelphia, with a return limit of thirty days in addition to date of sale.

All tickets must be validated by a special railroad agent at the Philadelphia headquarters in the Municipal Auditorium from April 29–May 3.

SPECIAL TRAIN SERVICE

If a sufficient number of members apply, the following special trains will be operated to and from the Philadelphia Session. Apply to the Executive Secretary of the College, or to the ticket agent of one of the participating roads, for further information.

Special Train from Chicago

Baltimore & Ohio R R

(Going)

| | |
|--|------------------------|
| Lv Chicago (B & O R R) | 10 00 A M C T—April 28 |
| Lv Chicago (63rd Street Station) | 10 25 A M C T—April 28 |
| Lv South Chicago | 10 45 A M C T—April 28 |
| Lv Gary, Ind | 11 02 A M C T—April 28 |
| Ar Garrett, Ind | 1 19 P M C T—April 28 |
| Lv Garrett, Ind | 2 22 P M E T—April 28 |
| Lv Defiance | 3 17 P M E T—April 28 |
| Lv Deshler | 3 54 P M E T—April 28 |
| Lv Cleveland (B & O R R) | 2 50 P M E T—April 28 |
| Ar Akron (Union Station) | 4 25 P M E T—April 28 |
| Lv Akron | 7 03 P M E T—April 28 |
| Lv Youngstown | 8 22 P M E T—April 28 |
| Lv Newcastle, Pa | 8 54 P M E T—April 28 |
| Lv Pittsburgh, Pa (P & L E Smithfield Station) | 10 25 P M E T—April 28 |
| Lv McKeesport, Pa | 10 59 P M E T—April 28 |
| Lv Connellsville, Pa | 12 03 A M E T—April 29 |
| Ar Philadelphia | 8 53 A M E T—April 29 |

Special Service from St Louis

| | |
|---|--------------------|
| Lv St Louis (B & O R R) | 9 15 A M—April 28 |
| Lv Vincennes | 12 20 P M—April 28 |
| Lv Mitchell, Ind | 1 45 P M—April 28 |
| Lv Louisville (B & O R R) | 1 25 P M—April 28 |
| Ar Cincinnati | 5 45 P M—April 28 |
| Lv Cincinnati (B & O R R) | 6 00 P M—April 28 |
| Lv Winton Place | 6 10 P M—April 28 |
| Lv Oakley, Ohio | 6 21 P M—April 28 |
| Lv Chillicothe | 8 20 P M—April 28 |
| Lv Parkersburg, W Va (Sixth St Station) | 10 35 P M—April 28 |
| Lv Clarksburg | 12 45 A M—April 29 |
| Lv Washington, D C | 8 00 A M—April 29 |
| Lv Baltimore, Md (Camden Station) | 8 44 A M—April 29 |
| Lv Baltimore, Md (Mt Royal Station) | 8 50 A M—April 29 |
| Ar Philadelphia | 10 48 A M—April 29 |

In view of the uncertainty at this time as to those who may desire to return in group parties, it is thought advisable to wait until after arrival at the convention to ascertain what special services for the return trip will be required.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5 00 P M, Thursday, May 2, immediately following the general scientific program.

of the afternoon All Masters and Fellows of the College are urged to be present

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary and the induction to office of the new President, Dr James Alex Miller, New York, New York

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated Special meetings will be announced and posted

COMMITTEE ON CREDENTIALS

Sunday, April 28, 10 00 A M Room 103, Exhibition Floor, Municipal Auditorium

BOARD OF REGENTS

Room 200, Lobby, Municipal Auditorium

Sunday, April 28, 2 00 P M

Tuesday, April 30, 12 00 M *

Friday, May 3, 12 00 M *

BOARD OF GOVERNORS

Room 200, Lobby, Municipal Auditorium

Monday, April 29, 5 00 P M

Wednesday, May 1, 12 00 M *

* Buffet luncheon served

SPECIAL FEATURES

MONDAY, APRIL 29, 1935

THE ANNUAL SMOKER—Immediately following the scientific program, at ten-thirty o'clock, Monday evening, in the main Ballroom of the Benjamin Franklin Hotel An unusual program of entertainment and music will be given by the Orpheus Club of Philadelphia

Among the features will be Dr Alberto Bimboni and Mr Ellis Hammond, piano duo, Mr John Ott and Mr Albert Zimmerman, piano and vocal song hits of the day, Mr H Tatnall Brown, Jr, impersonations, and many other interesting features

WEDNESDAY, MAY 1, 1935

CONVOCATION OF THE COLLEGE—8 15 P M, Ballroom, Benjamin Franklin Hotel All Masters and Fellows of the College and those to be received in Fellowship should be present Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in the Betsy Ross Room, mezzanine floor, Benjamin Franklin Hotel, at seven-thirty o'clock, preparatory to the formation of the procession They will occupy especially reserved seats in the central section of the ballroom to which they will be conducted by the Convocation marshall promptly at 8 15 As this is the most formal meeting of the College, it is suggested that all appear in evening dress

The Convocation is open to all physicians and their families generally, and to such of the general public as may be interested

Following the Convocation ceremony, the President will present the John Phillips Memorial Medal for 1934-35 Thereafter will follow the Convocational Oration, "The Thyroid Stimulating Hormone of the Anterior Pituitary Gland," by Dr Leo Loeb, Professor of Pathology, Washington University, St Louis

The President, Dr Jonathian C Meakins of Montreal, Canada, will then deliver the annual presidential address to the Masters Fellows and Associates of the College

The Presidential Reception in the Betsy Ross Room, mezzanine floor, will follow immediately after the program Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception All members and guests are invited to remain for dancing in the Grand Ballroom following the Reception

THURSDAY, MAY 2, 1935

THE ANNUAL BANQUET OF THE COLLEGE will be held at the Benjamin Franklin Hotel at 8 00 P M All members of the College and its Officers, physicians of Philadelphia and visitors attending the Session, with their families are invited to be present Consult the formal program to be printed later for announcements concerning the toastmaster and principal speakers

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The following program has been arranged with a view also to leave ample time for sight-seeing, shopping and recreation Complete lists of points of interest, principal shops, concerts and lectures will be issued by the local committee

The Franklin Room, Mezzanine Floor of the Benjamin Franklin Hotel, will be the headquarters for the visiting ladies

MONDAY, APRIL 29, 1935

Morning Registration (Franklin Room, Benjamin Franklin Hotel)

Afternoon 2 00 P M Sight-seeing trip of Philadelphia and Fairmount Park Tea at Strawberry Mansion one of the old historical houses Busses will leave from and return to the Benjamin Franklin Hotel

Evening 8 30 P M Lecture at the Planetarium, Franklin Institute, 20th St & The Parkway

10 30 P M Men's Smoker Ballroom Benjamin Franklin Hotel

TUESDAY, APRIL 30, 1935

Afternoon 1 30 P M Trip to Valley Forge Visit Rock Garden of Mr & Mrs Richard Haughton Paoli Tea at "Summerhill," Newtown Square, Residence of Mrs Alfred Stengel

Busses will leave from and return to the Benjamin Franklin Hotel

Evening The theatre optional

WEDNESDAY, MAY 1, 1935

Afternoon 1 00 P M As guests of the local committee, Luncheon at the Philadelphia Country Club followed by golf or bridge for those who care to play Busses will leave the Benjamin Franklin Hotel at 12 30 P M

Evening 8 15 P M Annual Convocation, Ballroom Benjamin Franklin Hotel All ladies are cordially invited

THURSDAY, MAY 2, 1935

Afternoon 1 30 P M As guests of the local committee, visit the green houses of Mr & Mrs Pierre duPont at "Longwood", Kennett Square, Pa

Cars will leave the Benjamin Franklin Hotel promptly

Evening 8 00 P M Annual Banquet, Ballroom, Benjamin Franklin Hotel

THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY, affiliated with the University of Pennsylvania, and located on the University campus at Thirty-

Sixth and Spruce Streets, will be open to Fellows of the College daily from 9 00 to 5 00 Dr Milton J Greenman, Director of the Institute, has kindly offered to arrange demonstrations of the work of the Institute

The work of the Institute is devoted to researches in neurology, genetics and animal behavior, and its laboratories will be open to the visits of our members

THE UNIVERSITY MUSEUM an institution devoted to the study of the history of mankind, particularly as represented by the remains of ancient civilizations, is open to all visitors daily, except Monday, from 10 to 5 Located at 34th and Spruce Streets within a block of the Municipal Auditorium, the Museum will be easily accessible to all attending the College meetings

The Museum contains collections obtained through various expeditions to many parts of the world, and is one of the outstanding Archeological Museums of the world

THE HALL AND LIBRARY OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA (22nd Street between Chestnut and Market Streets) will be open to visits and inspection by those attending the meeting of the American College of Physicians, daily from 10 to 5

Special displays of rare medical publications and medals, portraits and other objects of medical interest will be arranged for this occasion

The Librarian, Mr McDaniel, and members of the Library Committee will be at the Library to receive visitors and explain the displays

THE LIBRARY OF THE PENNSYLVANIA HOSPITAL is the oldest medical library in the United States It possesses many books of great historical interest and also other objects which date back to the earliest days of this very old hospital Exhibits in the Library will be arranged by Dr Francis R Packard and the Library will be open to members of the College each day during the clinical sessions from 9 00 A M to 1 00 P M

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the Exhibition Floor of the Municipal Auditorium

Exhibits consisting of medical literature and texts, pharmaceutical products, apparatus and appliances, special foods, etc , will be shown by the leading publishers and manufacturers The leading medical placement bureaus will also be among the exhibitors this year There will be many new exhibits not heretofore shown before the American College of Physicians

These exhibits afford an opportunity for physicians to examine the latest literature and the newest products in the field of medicine generally, their educational value should not be overlooked Every attendant at the Session is urged to visit each of the booths, for he will certainly find something new, interesting and scientifically valuable Intermissions in the general program have been arranged from Monday to Friday, inclusive, for the purpose of providing a definite time for the inspection of exhibits

GENERAL SESSIONS

The selection of the program for the General Sessions is a task of no small dimensions The response of the Fellows and friends of the College was most gratifying, in fact, it could almost be said embarrassing, as the number of contributions offered was several times greater than could possibly be accommodated in the comparatively short time at our disposal No attempt was made to arrange symposia although, as would be expected, many of the contributions lend themselves to an arrangement for viewing certain problems from different angles

Fundamental aspects of physiology and biochemistry have been given a place beside the more practical problems of medicine This serves the good purpose of throwing into relief the future trends of investigation towards the elucidation of our many difficulties

The *Diseases of Cardiovascular System* are principally discussed from the point of view of the peripheral circulation as distinct from the heart alone. The subject of vascular disease as influenced by other systemic disorders is particularly viewed from the standpoint of the diabetic, while at the same time the latest advances in carbohydrate metabolism are considered by one of the outstanding workers in this field.

Neurology has a place in the program not only in diseases of common occurrence and of great interest to the internist, but also there will be a communication dealing with the most fundamental modern aspects of neurologic physiology.

Endocrinology will be discussed from a number of aspects of interest both to the physician and the experimentalist. The most recent concepts of endocrine balance and unbalance and interlocking control by anti-hormone action are discussed by one of the greatest authorities and the pioneer in this subject. Other phases of endocrinology are also considered.

Diseases of the Lungs are covered from a number of angles. The increasing interest in the newer concepts of chronic pulmonary diseases of a non-tuberculous nature is catered to by a number of essayists. Other phases of this subject are reviewed and the latest results critically analyzed and placed before the Fellows and guests by those fully qualified for such an authoritative review. Of particular interest is a communication dealing with the processes of healing in collapse therapy.

Hematology is considered rather from the standpoint of taking stock of the present state of our knowledge of such important disorders of the hematopoietic system as the anemias in pregnancy, aplastic and agranulocytic angina. Much confusion reigns in certain phases of these subjects and it is intended that as far as possible order may be restored.

The papers on *Gastro-enterology* are chiefly concerned with the liver both from the experimental and clinical aspects. The mysteries of hepatic cirrhosis have been investigated. This subject was before the College some years ago but the present communications carry the subject some steps further in its elucidation.

Certain phases of *Infectious Diseases* and *Immunology* are dealt with and original and stimulating concepts are put forward.

The *Convocational Oration* will be delivered on Wednesday evening by Professor Leo Loeb, of St. Louis. Professor Loeb during a period of approximately forty years has contributed to many fields of general and experimental pathology. His researches have had a profound effect upon Medical Science and in particular his work on the thyroid stimulating hormone of the anterior hypophysis, which will be the subject of his address.

GENERAL INFORMATION
LIST OF PHILADELPHIA HOTELS

GENERAL HEADQUARTERS
MUNICIPAL AUDITORIUM

34th Street below Spruce

Registration headquarters, railroad office, information bureau, exhibits and the general assembly hall are all located here

HOTEL HEADQUARTERS
BENJAMIN FRANKLIN
HOTEL

9th and Chestnut Sts
The Benjamin Franklin Hotel will be the headquarters hotel for Officers, Regents, and Governors, and so far as facilities permit, will accommodate other members and guests of the College Reservations that the Benjamin Franklin Hotel cannot fill will be referred immediately to some other hotel conveniently local
Apply directly for reservations to the hotel of your choice Physicians are requested to mention specifically the fact that reservations are being made in connection with the Clinical Session of the American College of Physicians

| Name and Location | No of Rooms | RATES PER DAY | | | | | | SUITES |
|---------------------------------------|-------------|---------------------|--------------|----------------------|--------------|--|---------------|--------|
| | | ROOM— ONE PERSON | | ROOM— TWO PERSONS | | | | |
| | | With Bath | Without Bath | With Bath | Without Bath | | | |
| Benjamin Franklin, 9th and Chestnut | 1200 | \$3 50-5 00 | | \$5 00-8 00 | | | \$ 8 00-20 00 | |
| Adelphia, 13th and Chestnut | 400 | 3 50 up | | 5 00-8 00 | | | 10 00 | |
| Barclay, Rittenhouse Square E | 634 | 4 00 up | | 6 00 up | | | 10 00 | |
| Bellevue-Stratford, Broad and Walnut | 800 | 3 50-5 00 | 2 50-3 50 | 5 00-9 00 | 4 00-6 00 | | 15 00-20 00 | |
| Broadwood, Broad and Wood | 200 | 2 00 up | | 4 00 up | | | | |
| Colonial, 11th and Spruce | 100 | 2 50 up | 1 50-2 00 | 3 50-5 00 | 2 00-3 00 | | | |
| Drake, 1512 Spruce | 150 | 4 00 up | | 6 00 up | | | 5 50-8 00 | |
| Lorraine, Broad and Fairmount | 300 | 2 50-3 50 | 2 00-2 50 | 5 00-6 00 | 3 50-4 00 | | 10 00-12 00 | |
| McAlpin, 10th at Chestnut | 116 | 2 00 up | 1 50 | 4 00 up | 3 00-3 50 | | 5 00-8 00 | |
| Normandie, 36th and Chestnut | 234 | 2 50-3 00 | 2 00 | 3 50-4 00 | 3 00 | | 5 00-7 00 | |
| Pennsylvania, 39th and Chestnut | 600 | 2 50-5 00 | | 4 00-8 00 | | | 8 00-15 00 | |
| Rutz-Carlton, Broad and Walnut | 190 | 4 00-7 00 | | 7 00-9 00 | | | 10 00 | |
| Robert Morris, 17th and Arch and Pkwy | 208 | 2 50-4 00 | | 4 00-6 00 | | | | |
| Roosevelt, 23rd and Walnut | 150 | 2 50 | | 4 00 | | | 5 00-8 00 | |
| St James, 13th and Walnut | 178 | 2 50-3 50 | 2 00 | 4 00-6 00 | 3 50 | | 5 00-8 00 | |
| Stephen Girard, 2027 Chestnut | 100 | 2 50-3 50 | | 4 00-6 00 | | | 6 00-8 00 | |
| Sylvania, Juniper and Locust | 400 | 3 00 | | 5 00* | | | 12 00 up | |
| Walnut Park Plaza, 63d and Walnut | 520 | 3 00 | | 4 00-5 00 | | | 5 00-10 00 | |
| Walton, Broad and Locust | 350 | 2 50-4 50 | 2 00-2 50 | 4 00-7 00 | 3 50-4 00 | | 8 00-12 00 | |
| Warwick, 17th and Locust | 900 | 4 00 | | 6 00 | | | 10 00-15 00 | |
| Y W C A -Lincoln Hotel, 1222 Locust | 90 | 2 50 | 1 25-2 00 | 4 00 | 3 00 | | | |

* Extra large triple room, 3 beds, with bath or shower, \$6 00

* Extra large triple room, 3 beds, with bath or shower, \$6 00

OUTLINE OF SESSION

| TIME | MONDAY | TUESDAY | WEDNESDAY | THURSDAY | FRIDAY |
|-----------------------------|--|--------------------------------|--|--------------------------------|--------------------------------|
| | April 29 | April 30 | May 1 | May 2 | May 3 |
| 9 00 A M to 12 00 M | Morning free Registration, Exhibits, etc | Special Morning Lectures | Special Morning Lectures | Special Morning Lectures | Special Morning Lectures |
| | | 1st Clinical Session | 2nd Clinical Session | 3rd Clinical Session | 4th Clinical Session |
| 12 00 M to 2 00 P M | Luncheon | Luncheon | Luncheon | Luncheon | Luncheon |
| 2 00 P M to 5 30 P M | 1st General Session | 3rd General Session | 5th General Session | 6th General Session | 7th General Session |
| | | | | Annual Business Meeting | |
| 5 30 P M to 8 00 P M | Dinner | Dinner | Dinner | | |
| 8 00 P M to 11 00 P M | 2nd General Session followed by Smoker | 4th General Session | Convocation, followed by President's Reception and Dance | ANNUAL BANQUET | |

GENERAL SESSIONS

Philadelphia, Pa —April 29–May 3, 1935

OPENING GENERAL SESSION

Monday Afternoon, April 29, 1935

P M

- 2 00 Addresses of Welcome
 Alfred Stengel, General Chairman of the Nineteenth Annual Clinical Session
 J Norman Henry, Director of Public Health, City of Philadelphia
 Seth A Brumm, President, Philadelphia County Medical Society
 Response to Addresses of Welcome
 Jonathan C Meakins, President of the American College of Physicians
- 2 30 The Mechanism of the Lesions of Multiple Sclerosis
 Tracy J Putnam, Boston, Mass
- 2 55 The Nervous Control of the Heart and Blood Vessels
 Detlev W Bronk, Philadelphia, Pa
- 3 20 Creatine Metabolism in Muscle Disease
 A T Milhorat and H G Wolff, New York, N Y
- 3 40 The Diagnosis and Treatment of Myasthenia Gravis
 Walter M Boothby, Rochester, Minn
- 4 05 INTERMISSION
- 4 25 The Experimental Effects of Anterior Pituitary Hormones on Cranial Growth, and their Significance in Clinical Medicine
 Hector Mortimer, Montreal, Que
- 4 50 Personality and the Endocrines A Quantitative Study in 1400 Necropsies
 Walter Freeman, Washington, D C
- 5 10 The Fundamental Mechanism in the Production of Chronic Lymphatic Leukemia
 B K Wiseman and C V Moore, Columbus, Ohio
- 5 30 ADJOURNMENT

SECOND GENERAL SESSION

Monday Evening, April 29, 1935

Presiding Officer

James B Herrick, Chicago, Ill

P M

- 8 00 Studies on the Increased Metabolism in Hyperthyroidism
 E Cowles Andrus and Donald McEachern, Baltimore, Md
- 8 20 Internal or Visceral Myxedema
 Hans Lisser, San Francisco, Calif
- 8 40 Dissociation of the Thyroid from the Sympathetic Nervous System in the Treatment of Angina Pectoris and Congestive Heart Failure
 James Alex Lyon and Edmund Horgan, Washington, D C

- 9 05 Fatal Diabetic Coma with Acute Renal Failure
Maynard E. Holmes, Syracuse, N. Y.
- 9 25 Etiology and Sequelae of Acute Glomerular Nephritis A Study of 136 Cases
Francis D. Murphy, Milwaukee, Wis.
- 9 45 Growth and Development of Function in Blood Vessels and Lymphatics
(Motion Picture)
E. R. Clark, Philadelphia, Pa.
- 10 05 ADJOURNMENT

10 30 o'Clock

SMOKER

Ballroom, Benjamin Franklin Hotel

The Orpheus Club of Philadelphia will present a program of entertainment of unusual merit

THIRD GENERAL SESSION

Tuesday Afternoon, April 30, 1935

Presiding Officer

C. Hartwell Cocke, Asheville, N. C.

P. M.

- 2 00 Etiology of the Pulmonary Fibroses and Medico-Legal Aspects of Pneumoconiosis
Wm. S. McCann, Rochester, N. Y.
- 2 20 The Experimental and Pathological Aspects of Silicosis
Dudley Irwin, Toronto, Ont.
- 2 40 Basic Points in X-Ray Studies of Lung Anatomy and Pathology
John H. Skavlem and Kennon Dunham, Cincinnati, Ohio
- 3 00 Pulmonary Fibrosis and Emphysema
James Alex. Miller, New York, N. Y.
- 3 20 Oleothorax—Clinical and Experimental
John N. Hayes, Saranac Lake, N. Y.
- 3 40 INTERMISSION
- 4 00 Healing Mechanisms in Collapse Therapy
Max Pinner, Tucson, Ariz.
- 4 20 The Present Status of Artificial Pneumothorax in the Treatment of Lobar Pneumonia
S. S. Leopold and L. M. Lieberman, Philadelphia, Pa.
- 4 40 The Use of Helium as a New Therapeutic Gas in the Treatment of Asthma
Alvan L. Barach, New York, N. Y.
- 5 00 Accessory Sinus Infection Its Relation to Mastoid and Lung Infections
W. F. Manges, Philadelphia, Pa.
- 5 20 A Proposed Method of Evaluation of the Therapeutic Potency of Substances Effective in Pernicious Anemia and Its Application to Treatment
Bernard M. Jacobson and Cyrus Fiske, Boston, Mass.
- 5 35 ADJOURNMENT

FOURTH GENERAL SESSION

Tuesday Evening, April 30, 1935

 Presiding Officer

Francis M Pottenger, Monrovia, Calif

-
- P M
- 8 00 Further Studies on the Thymus and Pineal Glands (Motion Picture)
L G Rowntree, Philadelphia, Pa
- 8 25 Recent Work on Anti-Hormones
J B Collip, Montreal, Que
- 8 50 Medullary Tumors of the Adrenal Glands
M C Pincoffs, Baltimore, Md
- 9 10 Hypothyroidism A Common Symptom
Roger I Lee, Boston, Mass
- 9 30 Correlations of the Endocrine System
David L Thomson, Montreal, Que
- 10 00 ADJOURNMENT
-

FIFTH GENERAL SESSION

Wednesday Afternoon, May 1, 1935

 Presiding Officer

John H Musser, New Orleans, La

-
- P M
- 2 00 The Relationship of the Flat Chest to Physical and Mental Development
(Illustrated by Slides and Motion Pictures)
S A Weisman, Minneapolis, Minn
- 2 30 Immunological Application of Placental Extracts
Charles F McKhann, Boston, Mass
- 2 50 Experimental Studies Relating Vitamin "C" Deficiency to Rheumatic Fever
and Rheumatoid Arthritis
James F Rinehart, San Francisco, Calif
- 3 15 Further Observations on the Treatment of Chronic Rheumatoid Arthritis
with Streptococcal Vaccine
Charles W Wainwright, Baltimore, Md
- 3 30 INTERMISSION
- 3 50 Von Gierke's Glycogen Disease
L M Lindsay, Montreal, Que
- 4 10 Alterations in Hepatic Function Produced by Experimental Liver Lesions
Jesse L Bollman, Rochester, Minn
- 4 30 Clinical Observations on Some Phenomena Associated with Chronic Liver
Damage
A M Snell, Rochester, Minn
- 4 50 An Instance of Possible Cirrhosis of the Liver Induced by a Hair Tonic Con-
taining Carbon-tetrachloride
B B Vincent Lyon, Philadelphia, Pa

- 5 10 Incidence of Crateriform Ulcers of the Duodenum A Roentgenologic and
Pathologic Study
B R Kirklin and H A Burch, Rochester, Minn
5 30 ADJOURNMENT
-

ANNUAL CONVOCATION

Wednesday Evening, May 1, 1935

8 15 o'Clock

Ballroom Benjamin Franklin Hotel

The general profession and the general public are cordially invited No special admission tickets will be required

- 1 Convocation Ceremony
 - 2 Presentation of the John Phillips Memorial Medal
 - 3 Convocational Oration "The Thyroid Stimulating Hormone of the Anterior Pituitary Gland"
Leo Loeb, Professor of Pathology, Washington University, St Louis, Mo
 - 4 Presidential Address
Jonathan C Meakins, Montreal, Que
-

*Presidential Reception**Betsy Ross Room, Benjamin Franklin Hotel*

The Reception will follow immediately after the program Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception

Dancing

SIXTH GENERAL SESSION

Thursday Afternoon, May 2, 1935

Presiding Officer

James Alex Miller, New York, N Y

P M

- 2 00 Lymphedema of the Extremities Etiology, Classification and Treatment
E V Allen and R K Ghormley, Rochester, Minn
2 20 Cardiac Output in Common Clinical Conditions, and the Diagnosis of Myo-
cardial Insufficiency by Cardiac Output Methods
Isaac Starr, Jr, and C J Gamble, Philadelphia Pa
2 40 Studies on Cardiac Hemodynamics in Hypertension
J Murray Kinsman, Louisville, Ky

- 3 05 Acute Cor Pulmonale
Paul D White, Boston, Mass
- 3 20 Etiology and Prevention of Anemia in Pregnancy
Maurice B Strauss, Boston, Mass
- 3 40 INTERMISSION
- 4 00 Clinical Course and Pathological Changes in Aplastic Anemia
C P Rhoads, New York, N Y
- 4 20 Diagnosis and Treatment of Agranulocytic Angina
Henry Jackson, Jr, Boston, Mass
- 4 45 ADJOURNMENT

The *Annual General Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Official reports from the Executive Secretary and Treasurer will be read, new Officers, Regents and Governors will be elected, and the President-Elect, Dr James Alex Miller, will be inducted into office.

Thursday Evening, 8 00 o'Clock

Ballroom, Benjamin Franklin Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

The Toastmaster and the Guest Speakers will be announced in the Final Program

FINAL GENERAL SESSION

Friday Afternoon, May 3, 1935

Presiding Officer

David P Barr, St Louis, Mo

P M

- 2 00 A Study of the Comparative Vascular Disease in Patients with Obesity and Obese Patients with Diabetes
Byron D Bowen, Edgar Beck, James Fowler, and Edward Koenig, Buffalo, N Y
- 2 25 Arteriosclerosis and Hypertension in Diabetes
Howard F Root, Boston, Mass
- 2 40 Does the High Carbohydrate-Low Calorie Diet Prevent Arteriosclerosis in Diabetics?
I M Rabinowitch, Montreal, Que
- 3 05 Clinical Relationships of Blood Cholesterol with a Summary of our Present Knowledge of Cholesterol Metabolism
Lewis M Hurvath, Boston, Mass

3 30 INTERMISSION

3 50 The Conservative Treatment of Gangrene and Infections in the Lower Extremities of Diabetics

E H Mason, Montreal, Que

4 10 Treatment of Peripheral Vascular Diseases by Means of Suction and Pressure
Eugene M Landis and Lewis H Hitzrot, Philadelphia, Pa

4 30 Recent Advances in Carbohydrate Metabolism, with Particular Reference to Diabetes Mellitus

C N H Long, Philadelphia, Pa

4 50 The Treatment of Syphilis Complicating Tuberculosis

C Walter Clarke, New York, N Y

5 15 ADJOURNMENT

PROGRAM OF MORNING LECTURES

With Lantern Slide and Moving Picture Demonstrations

This course of morning lectures is a new feature on the program of the Clinical Sessions of the College. The course is presented as an elective, as a whole or for individual days, in place of the hospital clinics. These lectures will be presented daily, Tuesday to Friday, inclusive, from 9 30 to 11 30, in the lecture room on the Exhibit floor of the Municipal Auditorium, 34th Street below Spruce Street.

The Morning Lectures will be devoted to four general topics: Diseases of the Bones and Joints, Neurology, Bronchopulmonary Diseases and Endocrinology. The speakers will present their subjects with the aid of lantern slides, moving pictures and other demonstrations.

The lectures will be open to all members of the College, guests of the College, members of the College of Physicians of Philadelphia, members of the Philadelphia County Medical Society and senior students of the various medical schools of Philadelphia. Due to limited capacity, *special tickets*, similar to the clinic tickets, *must be procured at the Registration Desk*.

Tuesday Morning, April 30, 1935

MUNICIPAL AUDITORIUM

(S 34th St, below Spruce)

Lecture Room

Symposium on Diseases of the Bones and Joints

9 30-10 00 Roentgen Aspects of Bone Lesions

Henry K Pancoast and Philip J Hodes, Philadelphia, Pa

10 00-10 45 The Role of the Parathyroids in Diseases of the Bone

Fuller Albright, Boston, Mass

10 45-11 30 Arthritis: Etiologic Factors, Types and Treatment

Ralph Pemberton, Philadelphia, Pa

Wednesday Morning, May 1, 1935

MUNICIPAL AUDITORIUM
(S 34th St, below Spruce)

Lecture Room

Symposium on Neurology

- 9 30-10 00 Neurosurgical Measures for Relief of Pain
Francis C Grant, Philadelphia, Pa
- 10 00-10 30 Post-Encephalitic Behavior Problems in Childhood
Earl D Bond and Lauren H Smith, Philadelphia, Pa
- 10 30-11 00 Incipient Parkinsonism A Diagnostic Triad for its Early Recognition
A M Ornstein, Philadelphia, Pa
- 11 00-11 30 Regulation of Water Balance in the Symptomatic Treatment of Cerebral Disorders
Temple Fay, Philadelphia, Pa
-

Thursday Morning, May 2, 1935

MUNICIPAL AUDITORIUM
(S 34th St, below Spruce)

Lecture Room

Symposium on Newer Methods of Treatment of Pulmonary and Bronchial Disease

- 9 30-10 00 Indications, Technique and Results of Collapse Therapy in Pulmonary Tuberculosis
David A Cooper, Philadelphia, Pa
- 10 00-10 30 Oxygen Therapy in Pneumonia (Demonstration, Discussion of Indications and Results)
Leon H Collins, Jr, Philadelphia, Pa
- 10 30-11 00 The Bronchoscopic Treatment of Pulmonary Suppuration
Louis H Clerf, Philadelphia, Pa
- 11 00-11 30 Recent Advances in Thoracic Surgery
Richard H Meade, Philadelphia, Pa
-

Friday Morning, May 3, 1935

MUNICIPAL AUDITORIUM
(S 34th St, below Spruce)

Lecture Room

Symposium on Endocrinology

- 9 30-10 00 Interrelationships of the Endocrine Glands
Gerald T Evans, Philadelphia, Pa
- 10 00-10 30 A Lantern Slide Presentation of Endocrine Disorders
Hans Lissner, San Francisco, Calif
- 10 30-11 00 The Recognition and Treatment of Spontaneous Hyperinsulinism
Seale Harris, Birmingham, Ala

PROGRAM OF CLINICS

Tuesday, April 30, 1935

A 1

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Catherwood House

(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

- 9 00-10 00 Chorea
John P. Scott
- 10 00-10 30 Stovarsol in Treatment of Prenatal Syphilis
Donald M. Pillsbury and H. H. Perlman
- 10 30-11 00 Differentiation between Meningism and Meningitis
Charles F. McKhann, Boston, Mass
- 11 00-11 30 Diagnosis and Treatment of Pollen Asthma in Children, with Demonstration
S. C. Copeland
- 11 30-12 00 Continuous Venoclysis in Intestinal Intoxication of Infants, with Use of Glucose, Salts, Serum and Fat
Mitchell I. Rubin and Horace L. Hodes
-

A 2

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

(Entrance, Bainbridge Street below 18th)

Ward Walk

(Capacity, 10)

- 9 00-10 20 Ward Walk
Joseph Stokes, Jr
-

A 3

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease

(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

- 10 30-11 00 Demonstration of Influence of Diet upon Natural Resistance to Infection of Mice
Charles F. Church
- 11 00-11 30 Demonstration of Adrenalectomy in Rats Results of Treatment with Salts
Elizabeth Krick
- 11 30-12 00 Treatment in Convulsant Poisons
Joseph Stokes, Jr

Tuesday, April 30, 1935 (Continued)

**B 1 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

- 9 00- 9 30 Relief of Pericardial Constriction by Surgical Means Case Presentations
W Estell Lee and George C Griffith
- 9 30-10 00 Coronary Artery Disease
George Morris Piersol
- 10 00-10 30 Cure of Angina Pectoris by Section of the Posterior Thoracic Nerve
Roots
Francis C Grant and George C Griffith
- 10 30-11 20 Use of Digitalis and its Glucosides
William D Stroud
- 11 20-12 00 The Lymphoblastomas
Edward Steinfield
-

**B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

- 9 00- 9 20 Demonstration of the Anatomical Significance of the Cryptal Epithelium
in Tonsillar Infections
George B Wood
- 9 20- 9 40 Bronchosinusitis in Childhood
Howard Childs Carpenter
- 9 40-10 10 Factors Leading to Selective Collapse of the Lung Following Pneumo-
thorax
Richard T Ellison
- 10 10-11 00 Squint—Practical Demonstration for Orthoptic Training
Luther Peter
- 11 00-12 00 Selected Dermatologic Cases
Robert L Gilman and Sigmund S Greenbaum
-

**B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

Assemble at Private Admissions' Desk

Demonstrations and Ward Clinics

(Capacity, 15)

- 9 00-10 00 Lymphopathia Venerium—Proctologic Clinic
Collier Martin and Staff

Tuesday, April 30, 1935 (Continued)

- 10 00-12 00 Gastro-enterological Clinic
 (a) Sigmoidoscopic and Roentgenographic Demonstration of Cases of Ulcerative Colitis
 (b) Demonstration of Takata and other Liver Function Tests
 (c) Bile Microscopy in the Diagnosis of Gall Tract Disease
 H L Bockus, Henry Tumen, Harry Metzger and Striff
-

**C 1 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
 HOSPITAL**

(3400 North Broad Street)

Auditorium, 3d Floor, Medical Building

(Capacity, 250)

- 9 00- 9 30 Alternating Negative and Positive Pressures in the Treatment of Vascular Diseases
 Frank H Krusen
 9 30-10 00 Determination of Heart Size by Roentgenologic Methods
 Hugo Roesler
 10 00-10 30 The Nine Lead Electrocardiogram, Its Value in Angina Pectoris Preliminary Report
 Joseph B Wolffe
 10 30-11 00 Fundal Changes in the Hypertensive Diseases
 Walter I Lillie
 11 00-12 00 The Differentiation of Circulatory Failure of Peripheral and Cardiac Origin
 Arthur M Fishberg, New York, N Y
-

**C 2 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
 HOSPITAL**

(3400 North Broad Street)

Surgical Amphitheatre, 3d Floor, Hospital

(Capacity, 100)

- 9 00- 9 30 The Use of Iron and Arsenic in Secondary Anemias in Children
 Ralph M Tyson
 9 30-10 00 Newer Aspects of Pediatric Therapy
 H H Perlman
 10 00-10 30 The Relation between Psychoneurosis and Anorexia in the Young Child (Motion Picture Demonstration)
 Gerald H J Pearson
 10 30-11 00 Similarity of Throat Appearance in Diphtheria and Agranulocytosis
 Pascal F Lucchesi
 11 00-12 00 Discussion of Fluid Restriction Regime and Its Application to Pediatric Problems
 Temple Fay

C 3 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
 HOSPITAL
 (3400 North Broad Street)

(Capacity, 100)

- | | |
|-------------|---|
| 9 00- 9 30 | The Influence of Various Drugs on Allergic Reactions Louis Tuft and M L Brodsky |
| 9 30-10 00 | An Intradermal Test for Malignancy Benjamin Grushkin |
| 10 00-10 30 | Vaccination against Pneumococcus Infection with Special Reference to Pneumonia John A Kolmer |
| 10 30-11 00 | An Objective Method to Demonstrate Hyperalgesic Zones in Visceral Diseases Ernst Spiegel and Michael G Wohl |

X-Ray Museum, 6th Floor, Medical School Building
(Capacity, 50)

- | | |
|-------------|---|
| 9 00-10 30 | Chest Conference Bronchial Carcinoma, Bronchiectasis and Pulmonary Suppuration, Tuberculosis |
| | <i>Roentgenology</i> W Edward Chamberlain |
| | <i>Bronchoscopy</i> C L Jackson |
| | <i>Clinical Aspects</i> Edward Weiss |
| | <i>Chest Surgery</i> W Emory Burnett |
| | <i>Tuberculosis</i> Louis Cohen |
| | <i>Pathology</i> Frank W Konzelmann |
| 10 30-11 00 | Chronic Adhesive Pericarditis Hugo Roesler |

Outpatient Department, 2d Floor, Medical School Building
(Capacity, 20)

- 11 00-12 00 Demonstration of the Retinal Changes in Medical and Neurological
Conditions by Means of the Multicocular Ophthalmoscope
Walter I Lillie and Glen G Gibson

Tuesday, April 30, 1935 (Continued)

**C 6 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
 HOSPITAL**

(3400 North Broad Street)

Ward 3 C, Hospital

(Capacity, 15)

11 00-12 00 Ward Walk
 Roy L. Langdon

**C 7 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
 HOSPITAL**

(3400 North Broad Street)

(Unlimited—No Tickets Required)

11 00-12 00 Demonstrations and Exhibits in Various Departments of the Hospital
 and Medical School—Special Hospital Program will be available

**D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
 (36th and Spruce Streets)**

Medical Clinic

(Capacity, 175)

9 00- 9 45 Medical Diagnostic Clinic
 O. H. Perry Pepper
9 45-10 15 Clinic on Diabetes with Special Reference to the Course of the Disease
 as Influenced by Treatment
 Russell Richardson
10 15-10 45 Some Considerations Dealing with Pyrexia
 J. Harold Austin
10 45-11 00 Clinical Vitamin B Deficiency
 Katherine O'S. Elsom
11 00-12 00 X-Ray Conference
 Henry K. Pincus and Ward Physicians on Service

**D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
 (36th and Spruce Streets)**

Bronchoscopic Clinic

(Capacity, 100)

9 00- 9 30 Clinic on Renal Function
 Eugene M. Landis
9 30-10 00 Recent Advances in the Knowledge of Heart Sounds
 Alexander Margolies
10 00-10 30 Glycosuria—Diabetic and Non-Diabetic Case Presentations
 Leon Jonas
10 30-10 45 Follow-up Study of Patients Diagnosed as Neuroses
 Bernard I. Comroe

Tuesday, April 30, 1935 (Continued)

- 10 45-11 00 Peripheral Type of Facial Palsy in Vascular Conditions Case Presentation
J Q Griffith, Jr
- 11 00-12 00 Pulmonary Complications following Surgical Operations
Gabriel Tucker
-

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a

- 9 00-10 30 Ward B
Lewis H Hitzrot

D 3b

- 9 00-10 30 Ward D
T Grier Miller

D 3c

- 9 00-10 30 Pepper Ward
Francis C Wood

These above groups will alternate for the three following sets of demonstrations

Demonstrations in Maloney Clinic

- 10 30-11 00 8th Floor
Relation between Adrenals, Pituitary Body and Diabetes Mellitus
C N H Long and Staff
6th Floor, Department of Biophysics
Use of Short Wave Diathermy in Internal Medicine
D W Bronk and J P Herbey
3d Floor, Gastro-intestinal Department
Clinical Studies of Small Intestine
T Grier Miller and Staff
- 11 00-11 30 Room 218
Immunity in Diabetes
Russell Richardson
Room 709
Complement Fixation in Amoebiasis Nature of Test, Value in Acute and Chronic States, Value of Cultural, Wet Smear and Complement Fixation Methods
James S Forrester
Room 709
New Method for Discovery of Sickie Cells in the Blood Method to Discover the Trait that Develops Sickie Cells, Method for Permanent Films, Some Clinical Data
James S P Beck

Tuesday, April 30, 1935 (Continued)

Room 701

Colorimetric Readings by the Method of Optical Filters (Photonic Cells) Determination of Hemoglobin, Blood Sugar, Phosphates, etc., New Procedure for the Measurement of Serum Volume

F William Sunderman

11 30-12 15 Room 311, Robbette Foundation

Demonstration of the Use of Chest Leads in Electrocardiography
This demonstration will be of interest only to those with some knowledge of Clinical Electrocardiography

Room 801

Determination of pH in Blood and Serum by the Glass Electrode

W C Stadie

5th Floor

Inspection of Department of Physiotherapy Discussion of various procedures

Josef B Nylin

D 4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL BUILDING

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

9 00- 9 15 Pituitary and Experimental Hypothyroidism

Isolde T Zeckwer

9 15- 9 30 Experimental Anemia of Renal Insufficiency

Neil McLeod

9 30- 9 55 Experiments on Chemotropism of Human Leukocytes and Lymphocytes

Morton McCutcheon and H M Dixon

9 55-10 20 Adenocarcinoma in Frogs Possibly Associated with a Filterable Virus

Baldwin Lucke

10 20-10 30 Iron Balance in Experimental Anemia in Dogs

Elizabeth D Wilson

10 30-12 00 Demonstrations in Department of Pathology Room 264

(1) Demonstrations of above Papers

The Staff

(2) Gross Specimens

Dale R Coman et al

(3) Demonstration of Gross and Microscopic Specimens illustrating various Forms of Bone Disease

George Wagoner

Demonstrations from Department of Research Dermatology

(1) Torulosis

(2) Xanthomatosis

Fred D Weidman

There will also be demonstrations open to inspection from 9 00 to 12 00 in the Departments of Bacteriology and Research Surgery

Tuesday, April 30, 1935 (Continued)

E 1

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Amphitheatre
(Capacity, 100)

- 9 00- 9 30 Leukemia
Frederick L. Hartmann
9 30-10 00 Status Thymicolymphaticus
Edward H. Campbell
10 00-10 30 Clinic on Diseases of the Skin
John B. Ludy
10 30-11 00 Treatment of Epithelioma
Robert Shoemaker, 3d
11 00-12 00 Oxygen Therapy in Pneumonia, Cardiac and Cardiorespiratory Disturbances
Alvan Barach, New York, N. Y.

E 2

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Nurses' Lecture Hall
(Capacity, 50)

- 9 00- 9 30 Human Infertility Modern Treatment
Bradford Green
9 30-10 00 Dysmenorrhea Discussion of Hormone Therapy
Ross B. Wilson
10 00-10 30 Non-allergic Vasomotor Rhinitis and Underlying Emotional Factors
Ralph Butler and Clarence A. Patten
10 30-11 00 Emotional Factors and the Allergic State
Harry B. Wilmer
11 00-11 30 Obesity in Children Treatment
Julian M. Lyon
11 30-12 00 Obesity in Adults Dinitrophenol
Edward L. Bortz

E 3

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)
Men's Medical Ward, Second Floor

(Capacity, 15)

- 11 00-12 00 Ward Rounds
Frederick L. Hartmann

F

HAHNEMANN MEDICAL COLLEGE AND HOSPITAL
(Broad Street above Race)

Elkins Amphitheatre, 3d Floor
(Capacity, 200)

- 9 00- 9 45 Dermatological Clinic
Ralph Bernstein and Paul Wittman

Tuesday, April 30, 1935 (Continued)

- 9 45-10 30 Diagnosis and Treatment of Thyroid Deficiency
Lewis M Hurvath, Boston, Mass
- 10 30-11 00 Pituitary Dysfunction with Infantile Gonadism
Donald R Ferguson
- 11 00-12 00 Clinicopathological Conference
Samuel W Sappington
-

G 1 **PHILADELPHIA GENERAL HOSPITAL**
(34th Street below Pine)

Auditorium
(Capacity, 200)

- 9 00- 9 35 Superior Sulcus Tumors
Henry K Pancoast
- 9 35-10 20 Pulmonary Carcinoma
Herbert Lund, Bernard Widmann and Herman W Ostrum
- 10 20-10 40 Orthostatic Hypotension
Truman G Schnabel
- 10 40-11 05 High Blood Urea Nitrogen not due to Chronic Glomerulonephritis
Raymond Brust
- 11 05-11 20 Roentgenological Studies
(1) The Bones in Diseases of the Ductless Glands
(2) Pulmonary Lesions Simulating Tuberculosis
Herman W Ostrum
- 11 20-11 30 The Accuracy of Clinical Diagnoses Based on 1100 Consecutive Post-mortems
Jefferson H Clark
- 11 30-12 00 Obesity with Especial Reference to Salt Water Retention
Michael G Wohl
-

G 2 **PHILADELPHIA GENERAL HOSPITAL**
(34th Street below Pine)

Clinical Amphitheatre
(Capacity, 250)

- 9 00- 9 30 Studies of the Myopathies from a Chemical Pathological and Experimental Standpoint
John G Reinhold, M George Kingsley and R P Custer
- 9 30-10 30 Muscular Affections
J W McConnell
Walter M Boothby, Rochester, Minn
- 10 30-10 40 Non-stenosing Esophageal Carcinoma
R W Mathews
- 10 40-11 30 The Reticuloendothelial System and its Relation to Disease
R P Custer
- 11 30-12 00 Mercury Intoxication Treated by Sodium Formaldehyde Sulphoxylate
William Egbert Robertson

Tuesday, April 30, 1935 (Continued)

G 3**PHILADELPHIA GENERAL HOSPITAL**

(34th Street below Pine)

Medical Section Building

(Capacity, 15)

9 00-10 00 Ward Walk
Howard W. Schaffer

H 1**PRESBYTERIAN HOSPITAL**

(39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

9 00- 9 50 Changing Views on Arterial Hypertension
Joseph Barach, Pittsburgh, Pa
9 50-10 35 Pneumothorax in Lobar Pneumonia
Thomas Klein
10 35-11 15 Neurological Clinic Parkinsonian Syndrome in Chronic Epidemic
Encephalitis
Williams B. Cadwalader and Samuel Hadden
11 15-12 00 Sickle Cell Anemia
Truman G. Schnabel

H 2**PRESBYTERIAN HOSPITAL**

(39th Street and Powelton Avenue)

Ladies Aid Room

(Capacity, 65)

9 00- 9 30 Quantitative Methods of Testing Deafness
Douglas Macfarlan
9 30-10 00 Yeast Infections of the Mouth and Throat
Douglas Macfarlan
10 00-10 30 Neutrophilic Response to Infections of the Upper Respiratory Tract
Walter Cariss
10 30-12 00 Clinical-Pathological Conference
Aortic Aneurysms
George C. Griffith, Mary Easby and Kenneth E. Fowler
Femoral Aneurysms
Ernest Williamson and Kenneth E. Fowler

H 3**PRESBYTERIAN HOSPITAL**

(39th Street and Powelton Avenue)

Medical Ward

(Capacity, 15)

9 30-10 30 Ward Rounds
J. T. Beardwood, Jr., and Herbert T. Kelly

At 10 30 those making ward rounds may join the Clinical-Pathological Conference in the Ladies Aid Room

Tuesday, April 30, 1935 (Continued)

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL
(111 North 49th Street)

No Program on Tuesday

K 1 JEFFERSON HOSPITAL
(10th and Sansom Streets)

Clinical Amphitheatre
(1020 Sansom Street)

(Capacity, 250)

- 9 00- 9 30 Purpura Hemorrhagica Experimental and Pathological
Leandro Tocantins
- 9 30-10 00 Purpura Hemorrhagica Surgical and Medical Treatment
Harold W Jones
- 10 00-11 00 (1) Control of the Growth of Bones in the Lower Extremities
(2) Mechanical Factors in Low Back Pain
(3) Treatment of Poliomyelitis
J Torrance Rugh
- 11 00-11 30 Diagnostic Significance of Shoulder Top Pain
Fred J Kaltefleiter
- 11 30-12 00 Familial Rheumatic Fever
Edward J G Beardsley
-

K 2 JEFFERSON HOSPITAL
(10th and Sansom Streets)

Second Floor Medical

(Capacity, 15)

- 11 00-12 00 Ward Walk
Murtin E Rehfuess
-

L 1 PENNSYLVANIA HOSPITAL
(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Hospital Chapel

(Capacity, 200)

- George W Norris presiding
- 9 00-10 00 The Role of the X-Ray in the Diagnosis and Supervision of Tuberculosis
F Maurice McPhedran, Henry Phipps Institute, University of Pennsylvania
- 10 00-11 00 Clinic on Pulmonary Tuberculosis
James Alex Miller, New York, N Y
- 11 00-11 30 The Physiological Disturbances Produced by an Arteriovenous Aneurysm
Louis B Laplace

Tuesday, April 30, 1935 (Continued)

11 30-12 00 Matas Obliterative Aneurysmorrhaphy (Motion Picture)
W Estell Lee

9 00-1 00 P M The Library of the Pennsylvania Hospital, which is the first
Medical Library of this country, will be open from 9 00 until
1 00 daily Dr Francis R Packard is in charge of arranging
this exhibit

L 2

PENNSYLVANIA HOSPITAL

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Surgical Clinic

(Capacity, 200)

David L Farley presiding

9 00- 9 30 Analysis of Cases of Pellagra Admitted to the Pennsylvania Hospital
during the Past Ten Years

Thomas C Garrett

9 30-10 00 Lymphogranuloma Inguinale and its Relation to Rectal Stricture

Joseph V Vander Veer

10 00-11 00 Medical Clinic

James H Means, Boston, Mass

11 00-11 30 Cirrhosis of the Liver

W Grady Mitchell

11 30-12 00 Fever of Obscure Origin

David L Farley

L 3

PENNSYLVANIA HOSPITAL

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Ward Rounds

1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

9 00-10 00 Wards 3 and 4

David L Farley and Associates

L 3b

9 00-10 00 Wards 1 and 4

Thomas McCabe, Robert P Regester and Associates

Two above groups will consolidate for balance of program

Ayer Clinical Laboratory

(Capacity, 24)

10 00-11 00 Clinicopathological Conference

John T Bauer

Discussion, opened by Esmond R Long

Tuesday, April 30, 1935 (Continued)

Outpatient Department

- 11 00-11 30 Children's Heart Clinic Demonstration
Thomas M. McMillin
11 30-12 00 The Administration of a Hospital Outpatient Department
Samuel Bradbury
-

Wednesday, May 1, 1935

A 1

CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Catherwood House
(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

- 9 00-10 00 The Antirachitic Effect of Evaporated and Liquid Irradiated Milk
A Controlled Study
Joseph Stokes Jr.
10 00-10 30 The Results of the Use of Ascorbic Acid
Milton Rapoport
10 30-11 00 The Use of Molar Sodium Lactate in Diabetic Coma
Horace L. Hodes
11 00-12 00 The Modern Treatment of Squint
A. G. Fewell
-

A 2

CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

(Entrance, Bainbridge Street below 18th)

Ward Walk

(Capacity, 10)

- 9 00-10 20 Ward Walk
Mitchell I. Rubin
-

A 3

CHILDREN'S HOSPITAL
(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease
(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

- 10 30-11 00 Lyophilic Serum
Aims C. McGuinness
11 00-11 30 Demonstration of Rats Exhibiting Fat Deficiency Syndrome
Dorothy V. Whipple
11 30-12 00 Essential Hypertension in Children, with Demonstration of Pathological
Specimens
James J. Reilly and Irving J. Wolman

Wednesday, May 1, 1935 (Continued)

**B 1 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

- 9 00- 9 40 Diagnosis and Treatment of Cancer of Bladder
George Pfahler
- 9 40-10 20 Posture in Relation to Diagnosis Case Presentations
William Bates and John Howell
- 10 20-11 00 The Relation of Calcium-Phosphorus Metabolism to Certain Bone
Diseases
(a) Theoretical and Experimental Aspect
George Wagoner
(b) Clinical Aspect
DeForest P Willard
- 11 00-12 00 Pulmonary Emphysema
Henry M Thomas, Jr, Baltimore, Md
-

**B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

- 9 00- 9 40 Determination of the Phagocytic Power of Whole Blood or Plasma-
leukocyte Mixtures for Clinical or Experimental Purposes
Fred Boerner and Stuart Mudd
- 9 40-10 30 Rectal Stricture due to Lymphopathia Venerium
Collier Martin
- 10 30-11 00 Advisability of Medical Examination Preliminary to Gynecologic
Operation
William R Nicholson and Henry Tumen
- 11 00-12 00 Diagnosis and Treatment of Functional Menstrual Disorders Demon-
stration of Patients
Charles Mazer
-

**B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

Assemble at Private Admissions' Desk

Demonstrations and Ward Clinics

(Capacity, 15)

- 9 00-10 00 Gastroscopic Clinic
Gabriel Tucker
- 10 00-11 00 Roentgenologic Consideration of Interesting Gastro-intestinal Cases
Karl Kornblum

11 00-12 00 Ward Clinic, Neurological Cases
Clarence A. Patten

(Capacity, 250)

- | | |
|-------------|---|
| 9 00- 9 45 | Vaccination against Acute Poliomyelitis John A. Kolmer |
| 9 45-10 15 | Recent Progress in the Prevention and Treatment of Eclampsia Jesse O. Arnold |
| 10 15-11 00 | Clinicopathologic Conference The Evolution of Chronic Glomerulonephritis Including a Discussion of the Fundal Changes Edward Weiss, Frank W. Konzelmann, Walter I. Lillie and Glen G. Gibson |
| 11 00-12 00 | Nephrosis William S. McCann, Rochester, N. Y. |

(Capacity, 100)

- | | |
|-------------|--|
| 9 00- 9 30 | Bronchial Carcinoma Bronchoscopic Biopsy C L Jackson and Frank W Konzelmann |
| 9 30-10 00 | Hoarseness Laryngofissure for Early Carcinoma of the Larynx Chevalier Jackson |
| 10 00-10 30 | Laryngectomy for Carcinoma of the Larynx W Wayne Babcock |
| 10 30-11 00 | The Behavior of Cavities in Pulmonary Tuberculosis A J Cohen |

(Capacity, 100)

- | | |
|-------------|--|
| 9 00- 9 30 | Vertigo with Special Reference to Cortical Localization of the Labyrinth Ernst Spiegel |
| 9 30-10 15 | The Mechanism of Headache Its Analysis and Treatment Temple Fay |
| 10 15-11 00 | The Hydrostatics and Hydrodynamics of the Cerebrospinal Fluid System with Special Reference to Encephalography W Edward Chamberlain and Nicholas Gotten |

Wednesday, May 1, 1935 (Continued)

- 11 00-11 30 The Diagnosis of Tumors of the Brain
Nathaniel W Winkelman
11 30-12 00 The Diagnosis of Intracranial Lesions from the Ophthalmological
Standpoint
Walter I Lillie
-

**C 4 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Department of Bronchoscopy, Hospital

(Capacity, 20)

- 11 00-12 00 Demonstration Technique of the Instillation of Lipiodol for Bronch-
ography
C L Jackson
-

**C 5 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Outpatient Department, 1st Floor, Medical School Building

(Capacity, 20)

- 11 00-12 00 Biliary Drainage with Special Reference to Cytology and Parasitic
Infestation (Demonstration)
Charles-Francis Long and W A Swalm
-

**C 6 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Ward 2 C, Hospital

(Capacity, 15)

- 11 00-12 00 Ward Walk
Allen G Beckley
-

**C 7 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

(Unlimited—No Tickets Required)

- 11 00-12 00 Demonstrations and Exhibits in Various Departments of the Hospital
and Medical School—Special Hospital Program will be available

Wednesday, May 1, 1935 (Continued)

D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Medical Clinic

(Capacity, 175)

- 9 00- 9 45 Clinic on Pulmonary Actinomycosis
Sydney R. Miller, Baltimore, Md
- 9 45-10 15 Dwarfism Observations on Treatment Illustrative Cases
James E. Cottrell
- 10 15-10 45 Discussion of Possibility and Value of Desensitization in the Treatment of Arthritis
Herbert Fox
- 10 45-11 30 Heart Disease in Relation to Surgery
Alfred Stengel
- 11 30-12 00 Clinicopathological Conference
Baldwin Lucke and Medical Staff

D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bronchoscopic Clinic

(Capacity, 100)

- 9 00- 9 30 Clinic on Coronary Occlusion
Francis C. Wood
- 9 30-10 00 Oxygen Administration in Pneumonia
Leon H. Collins, Jr
- 10 00-10 15 Amyloid Nephrosis
F. William Sunderman
- 10 15-10 30 Irradiation Reactions in the Lungs
J. R. Andrews
- 10 30-10 45 Renal Changes in Hyperparathyroidism
Kendall Elsom
- 10 45-11 00 Spinal Cord Involvement in Hodgkin's Disease
Melbourne J. Cooper
- 11 00-11 15 Extrinsic Factors Influencing the Sedimentation Rate
Harry Flippin
- 11 15-11 30 Influence of Chest Deformities on the Heart and Great Vessels
Joseph Edeiken
- 11 30-12 00 Certain Types of Cardiac Involvement Encountered in Coroner's Examinations, Observations on their Clinical Significance
Martin P. Crane

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a

- 9 00-10 30 Ward B
Thomas Fitz-Hugh, Jr

Wednesday, May 1, 1935 (Continued)

D 3b

9 00-10 30 Ward D
Simon S Leopold

D 3c

9 00-10 30 Pepper Ward
Eugene M Landis

*Three above groups will alternate for the three following
sets of demonstrations*

Demonstrations in Maloney Clinic

- 10 30-11 00 8th Floor
Relation between Adrenals, Pituitary Body and Diabetes Mellitus
C N H Long and Staff
6th Floor, Department of Biophysics
Use of Short Wave Diathermy in Internal Medicine
D W Bronk and J P Herbey
3d Floor, Gastro-intestinal Department
Clinical Studies of Small Intestine
T Grier Miller and Staff
- 11 00-11 30 Room 218
Immunity in Diabetes
Russell Richardson
Room 709
Complement Fixation in Amoebiasis Nature of Test, Value in Acute
and Chronic States Value of Cultural, Wet Smear and Comple-
ment Fixation Methods
James S Forrester
Room 709
New Method for Discovery of Sickle Cells in the Blood Method to
Discover the Trait that Develops Sickle Cells, Method for Per-
manent Films, Some Clinical Data
James S P Beck
Room 701
Colorimetric Readings by the Method of Optical Filters (Photronic
Cells) Determination of Hemoglobin, Blood Sugar, Phosphates,
etc , New Procedure for the Measurement of Serum Volume
F William Sunderman
- 11 30-12 15 Room 311, Robinette Foundation
Demonstration of the Use of Chest Leads in Electrocardiography
This demonstration will be of interest only to those with some
knowledge of Clinical Electrocardiography
Room 801
Determination of pH in Blood and Serum by the Glass Electrode
W C Stadie
5th Floor
Inspection of Department of Physiotherapy Discussion of various
procedures
Josef B Nylin

Wednesday, May 1, 1935 (Continued)

**D 4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL
BUILDING**

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

- 9 00- 9 20 A Study of Cystinuria
J C Andrews
- 9 20- 9 40 Rickets and Parathyroid Glands
J H Jones
- 9 40-10 00 Movements of Mammalian Fetuses (Motion Picture Demonstration)
E A Swenson
- 10 00-10 30 Motion Pictures of Circulation in the Rabbit's Ear
E R Clark and E A Swenson
- 10 30-12 00 Demonstrations in the Department of Anatomy
- (1) Microscopic Studies on Living Mammalian Blood Vessels and Other Tissues, in Transparent Chambers
E R Clark, E L Clark and Associates
 - (2) A Transparent Chamber Permitting Access for Cell Cultures, Transplantation, or Manipulations in the Living Mammal
R G Williams
 - (3) Models of the Basal Ganglia of the Human Brain
W H F Addison and Doris A Fraser
 - (4) Venous Circulation of the Skull, with Especial Reference to its Significance in Infections
O V Batson
 - (5) Microdissection of Living Cells
G S deReny
 - (6) Growth and Behavior of Living Nerve Cells in an Electric Field
S C Williams
 - (7) *a*—Changes in the Fish Retina after Cutting the Optic Nerve and Retinal Blood Vessels
b—The Effects of Pituitary Extracts on Sexual Activity in a Species of Fish
S A Matthews
 - (8) The Behavior of Tissue Culture Cells in the Presence of Amoebicidal Drugs
M J Hogue
 - (9) A Case of Pseudohermaphroditism in a Hyla (Specimen from Philadelphia Zoological Garden)
C D Van Cleave
 - (10) General and Local Structural Changes in the Intestine of the Rat when Fed Unbalanced, Artificial Diets
J L Wierda

There will also be demonstrations open to inspection from 9 00 to 12 00 in the Departments of Pathology, Bacteriology and Research Surgery

Wednesday, May 1, 1935 (Continued)

E 1

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Amphitheatre
(Capacity, 100)

- 9 00-10 00 Diabetes
I M Rabinowitch, Montreal, Que
- 10 00-10 30 Juvenile Diabetes
Walter M Bortz, Greensburg, Pa
- 10 30-11 00 Studies of the Peripheral Vascular System
William B Wartman
- 11 00-11 30 Treatment of Surgical Lesions in Diabetes
Damon B Pfeiffer and J Montgomery Deaver
- 11 30-12 00 Chronic Middle Ear Infection Diagnosis and Treatment
James A Babbitt
-

E 2

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Research Institute
(Capacity, 50)

- 9 00- 9 30 Importance of Cystine in Growth and Development
M A Bennett
- 9 30-10 00 The Oxidation Products of Cystine
Gerrit Toennies
- 10 00-10 30 Chemical Relations of Cholesterol, Carcinogenic Substances and Certain Hormones
Theodore F Lavine
- 10 30-11 00 Protection against Carcinogenesis afforded by Sulphydryl
Stanley P Reimann
- 11 00-11 30 Presentation of Precision Methods for Determining Sulphur
K Shinohara
- 11 30-12 00 Proteinuria
Grace Medes
-

E 3

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)
Men's Medical Ward, Second Floor

(Capacity, 15)

- 11 00-12 00 Ward Rounds
Edward L Bortz
-

F

HAHNEMANN MEDICAL COLLEGE AND HOSPITAL
(Broad Street above Race)

Elkins Amphitheatre, 3d Floor
(Capacity, 200)

- 9 00- 9 30 Clinical Problems in Pneumonia
E Roland Snader, Jr
- 9 30-10 15 Demonstration of the Taking of Intra gastric Temperature Curves and Intra gastric Photography
Harry M Eberhard

Wednesday, May 1, 1935 (Continued)

- 10 15-10 45 Total Thyroidectomy in Intractable Heart Failure
Milton J Raisbeck, New York, N Y
- 10 45-11 15 Non-Colloidal Sulphur in the Treatment of Arthritis
Lowell L Lane and Peter J Warter
- 11 15-12 00 Clinical Roentgenological Conference on Tuberculosis
George G Ornstein, New York, N Y
Joseph W Post
-

G 1 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Auditorium

(Capacity, 200)

- 9 00- 9 30 Cerebral Histamine as a Complication of Severe Systemic Disorders
Helena Riggs
- 9 30-10 15 Cerebral Vascular Disease
Clarence A Patten
- 10 15-11 00 Psychopathology in Internal Medicine
Edward A Strecker
- 11 00-11 15 Transcerebral Diathermy in Parkinsonism
Samuel Hadden and A A Maitucci
- 11 15-12 00 Changes in the Chemistry and Composition of the Blood in Mental States
Seymour DeWitt Ludlum
-

G 2 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Clinical Amphitheatre

(Capacity, 100)

- 8 00- 9 30 Aneurysm, Congestive Failure, Cardiac Pain and Peripheral Vascular Disease, their Surgical Aspects
W Wayne Babcock
- 9 30-10 30 Somatic Symptoms as Part of an Early Schizophrenic Reaction
O Spurgeon English
- 10 30-11 30 Endocrinopathies
Samuel A Loewenberg
- 11 30-12 00 Oral Diseases with Special Reference to Syphilis
Sigmund S Greenbaum
- 12 00-12 30 Multiple Neuritis
George Wilson
-

G 3 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Medical Section Building

(Capacity, 15)

- 10 00-12 00 Ward Walk
Fred J Kaltefleiter

Wednesday, May 1, 1935 (Continued)

G 4 PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)

Department of Metabolism

(Capacity, 25)

- 9 00-10 00 The Philadelphia General Hospital Method of Standardizing the
Diabetic
Reuben Davis
- 10 00-11 00 (a) Treatment of Diabetic Coma
(b) Cerebral Lesions Found in Six Uncomplicated Cases of Diabetic
Coma
W Wallace Dyer
- 11 00-12 00 (a) Results of Neglected Diabetes Mellitus
Edward S Dillon
(b) Presentation of Interesting Cases of Diabetes Mellitus
Lewis H Hitzrot
-

H 1 PRESBYTERIAN HOSPITAL
(39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

- 9 00- 9 50 Clinic on Hypertension
Louis Warfield, Milwaukee, Wis
- 9 50-10 20 Modified Tetralogy of Eisenmenger
James E Talley and Kenneth E Fowler
- 10 20-10 40 Cardiovascular Disease in Patients with Myomata
Ferdinand Fetter
- 10 40-11 20 Hyperthyroidism in Pregnancy
Collin Foulkrod and Frederick A Bothe
- 11 20-12 00 Electrocardiographic Studies in Pericardial Disease
George C Griffith
-

H 2 PRESBYTERIAN HOSPITAL
(39th Street and Powelton Avenue)

Ladies' Aid Room

(Capacity, 65)

- 9 00- 9 30 Value and Limitation of Tests for Pancreatic Function
Thomas Johnson
- 9 30-10 10 Glucose Tolerance Tests Methods, Value and Danger
Herbert T Kelly
- 10 10-10 30 Glucose Tolerance Tests in Epilepsy
Joseph R Pierson
- 10 30-12 00 Clinical-Pathological Conference
Endocarditis, Subacute, Bacterial
Truman G Schnabel and Kenneth E Fowler
Ruptured Heart
Thomas Klein and Kenneth E Fowler

Wednesday, May 1, 1935 (Continued)

H 3

PRESBYTERIAN HOSPITAL
(39th Street and Powelton Avenue)

Medical Ward

(Capacity, 15)

9 30-10 30 Ward Rounds
Thomas Klein

At 10 30 those making ward rounds may join the Clinical-Pathological Conference in the Ladies' Aid Room

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL
(111 North 49th Street)

Auditorium

(Capacity, 250)

- 9 00- 9 20 Introduction
Edward A. Strecker
- 9 20- 9 40 Medical Aspect of the Neuroses
Lauren H. Smith
- 9 40-10 00 Psychoanalytic-Medical Relationships
Kenneth E. Appel
- 10 00-10 20 Physiologic Factors in Psychiatric Research
Harold D. Palmer
- 10 20-10 40 The Response of the Spinal Cord to Two Stimuli
Joseph Hughes
- 10 40-11 00 Post-Encephalitic Behavior Disorders
Earl D. Bond
- 11 00-12 00 Historical Exhibit (Library of the Parent's Council) Books and
Curiosa Relating to Psychiatry
Clifford B. Farr
- Inspection of the Institute, Laboratories and Franklin School
-

K 1

JEFFERSON HOSPITAL
(10th and Sansom Streets)

Clinical Amphitheatre
(1020 Sansom Street)

(Capacity, 250)

- 9 00- 9 20 The Determination of the Liver Function in Diseases of the Biliary
Tract
A. Cantarow
- 9 20- 9 40 Differential Diagnosis of Diseases of the Liver
B. B. Vincent Lyon
- 9 40-10 00 Surgical Aspect of Diseases of the Liver
Charles F. Nassau
- 10 00-11 00 Clinicopathological Conference
Edward J. G. Beardsley, Baxter L. Crawford and Kenneth E. Fry

Wednesday, May 1, 1935 (Continued)

- 11 00-12 00 The Diagnosis and Treatment of Bronchiectasis
Roentgen Ray
 John T. Farrell, Jr.
Bronchoscopic
 Louis H. Cleif
Surgical
 John B. Flick
-

K 2

JEFFERSON HOSPITAL

(10th and Sansom Streets)

Curtis Clinic

(1015 Walnut Street)

Auditorium, 12th Floor

(Capacity, 170)

- 9 00- 9 20 A Phase of Arthritis
 Abraham Cohen
 9 20-9 40 Dermatological Aspects of Syphilis
 Abram Strauss
 9 40-10 00 Syphilis from the Urologist's Standpoint
 Stanley Q. West
 10 00-10 20 Neurological Aspects of Syphilis
 C. Fred Becker
 10 20-10 40 Medical Aspects of Syphilis
 Jacob Cahan
 10 40-11 00 Syphilis in Obstetrics
 Thaddeus L. Montgomery
 11 00-11 20 Treatment of Congenital Syphilis
 John Coppolino
 11 20-11 40 Occlusive Vascular Disease, Differential Diagnosis and Treatment
 David W. Kramer
 11 40-12 00 Larosidin in the Treatment of Peptic Ulcer
 John T. Eads
-

K 3

JEFFERSON MEDICAL COLLEGE

(1025 Walnut Street)

(Capacity, 75)

Department of Pharmacology, Room 420

- 9 00-10 00 Demonstration
 Action of Drugs on Small Intestine
 The Effect of Some Hormones upon the Uterus and Ovaries of
 the Cat
 Charles M. Gruber and John T. Brundage
 Department of Pathology, Auditorium
 10 00-11 00 Demonstration and Discussion
 The Shock Syndrome Its Genesis and Associated Pathology
 Virgil H. Moon

Wednesday, May 1, 1935 (Continued)

Department of Physiology, Room 410

11 00-12 00 Demonstration

Some Gastro-intestinal Reflexes

J Earl Thomas and Joseph O Crider

K 4

JEFFERSON HOSPITAL

(10th and Sansom Streets)

Second Floor Medical

(Capacity, 15)

11 00-12 00 Ward Walk

Ross V Patterson

L 1

PENNSYLVANIA HOSPITAL

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Hospital Chapel

(Capacity, 200)

Albert W Bromer presiding

Symposium on Rheumatic Fever

9 00- 9 40 The Results of Four Years' Experience in the Treatment of Rheumatic
Fever with Intravenous Streptococcus Vaccination

Albert W Bromer, New York, N Y

9 40-10 20 The Treatment of Children Under Eight Years of Age, with Rheumatic
Heart Disease, with Intravenous Streptococcus Vaccination

Francis Q Thorp and D Stewart Polk

10 20-11 00 Cardiac Pain with Special Reference to its Causes in Rheumatic Fever

Louis B Laplace

11 00-12 00 The Reaction of the Circulation to Exercise

David P Barr, St Louis, Mo

9 00- 1 00 P M The Library of the Pennsylvania Hospital, which is the first
Medical Library of this country, will be open from 9 00 until
1 00 daily Dr Francis R Packard is in charge of arranging
this exhibit

L 2

PENNSYLVANIA HOSPITAL

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Surgical Clinic

(Capacity, 200)

William D Stroud presiding

Cardiovascular Symposium

9 00- 9 40 The Effects of Acetyl-B-Methylcholin on Paroxysmal Tachycardia and
Peripheral Vascular Disease

John A Reisinger

Wednesday, May 1, 1935 (Continued)

- 9 40-10 10 Whole Leaf Digitalis as Compared to its Glucosides in the Treatment
of Cardiovascular Disease
William D Stroud
- 10 10-10 40 Verodigen, a Digitalis Glucoside
Joseph B Vander Veer
- 10 40-11 00 Digitalme Nativelle, a Digitalis Product
D W Leik
- 11 00-12 00 The Treatment of Cardiovascular Syphilis
John H Stokes and Associates
-

L 3**PENNSYLVANIA HOSPITAL**

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Ward Rounds

1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

- 9 00-10 00 Wards 3 and 4
David L Failey and Associates

L 3b

- 9 00-10 00 Wards 1 and 4
Thomas McCrae, Robert P Regester and Associates

Two above groups will consolidate for balance of program

Ayer Clinical Laboratory

(Capacity, 24)

- 10 00-11 00 Clinicopathological Conference
John T Bauer
Discussion, opened by Edward B Krumbhaar

Outpatient Department

- 11 00-11 30 Diabetes Clinic Demonstration
Garfield G Duncan
- 11 30-12 00 The Administration of a Hospital Outpatient Department
Samuel Bradbury

Thursday, May 2, 1935

A 1

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Catherwood House
(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

- 9 00-12 00 Combined Clinic on Non-Specific Infections of the Lung
John C. Gittings, Ralph D. Biemer, Edward H. Campbell, Gabriel
Tucker, Irving J. Wolman and Mitchell I. Rubin
-

A 2

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Ward Walk

(Entrance, Bainbridge Street below 18th)

(Capacity, 10)

- 9 00-10 20 Ward Walk
John P. Scott
-

A 3

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease
(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

- 10 30-11 00 Demonstration by Chritts of Reaction to Intramuscular Injection of
Whole Human Blood
Milton Rapoport
11 00-11 30 Demonstration of a Health Appraisal
Howard C. Carpenter
11 30-12 00 Congenital Heart Disease
Rachel Ash
-

B 1

GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

- 9 00- 9 20 Serum Phosphatase in the Differential Diagnosis of Jaundice
Maurice Rothman
9 20- 9 40 Takata Reaction in Hepatic Disease
Henry Tumen

Thursday, May 2, 1935 (Continued)

- 9 40-10 20 Clinic on Diseases of the Liver
A M Snell, Rochester, Minn
- 10 20-11 00 A Demonstration of the Diagnostic and Therapeutic Methods in the
Allergic Diseases, with Special Reference to the Unusual
H B Wilmer, John Murphy and Merle M Miller
- 11 00-11 20 Hypochloremia, Alkalosis with Azotemia and Dehydration
John Eiman and Walter G Karr
- 11 20-12 00 Clinicopathological Conference
Eugene Case and Members of Medical Staff
-

**B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**

(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

- 9 00- 9 40 Results of Neurosurgical Operations
Francis C Grant
- 9 40-10 10 Pneumocranium in the Treatment of Character Changes in Children
William Drayton
- 10 10-10 40 Acute Disseminated Encephalomyelitis with Motion Pictures, Case His-
tories and Neuropathological Specimens
Fred H Leavitt
- 10 40-11 10 Radiculitis and Neuritis Its Diagnosis and Treatment
Joseph C Yaskin
- 11 10-11 40 Treatment of Neurosyphilis Case Demonstration
Clarence A Patten
- 11 40-12 00 Cases Illustrating Maxillofacial Surgery
Robert Ivy
-

**B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**

(19th and Lombard Streets)

Assemble at Private Admissions' Desk

Demonstrations and Ward Clinics

(Capacity, 15)

- 9 00-10 00 Demonstration of Laboratory Procedures in the Diagnosis of Func-
tional Disturbances of the Generative Tract
Charles Mazer, A J Ziserman, and Adele Yamoof
- 10 00-11 00 Ward Rounds
George Morris Piersol
- 11 00-12 00 Cardiovascular Diseases
George C Griffith

Thursday, May 2, 1935 (Continued)

**C 1 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Auditorium, 3d Floor, Medical Building

(Capacity, 250)

- 9 00- 9 45 The Brain in General Infections and Toxemias
Nathaniel W Winkelman
- 9 45-10 30 Atrophy of the Frontal Lobes and Reversion to Infantile Behavior
Walter Freeman Washington D C
- 10 30-11 15 Clinico-psychiatric Conference Functional Disturbances of the Gastro-
intestinal Tract
Edward Weiss and O Spurgeon English
- 11 15-12 00 Anxiety States with Special Reference to Hyperventilation
William J Kerr, San Francisco, Calif

**C 2 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Surgical Amphitheatre, 3d Floor, Hospital

(Capacity, 100)

- 9 00- 9 30 A Consideration of Sinus Disease with Special Reference to the Cause
of Headache
Robert F Ridpath
- 9 30-10 00 Deafness from the Economic and Social Viewpoints
Matthew S Ersner
- 10 00-10 30 Feet in their Relationship to Some Problems of the Internist
John Royal Moore
- 10 30-11 00 Studies on the Physiological Effects of Fever Produced by Physical
Means
Frank H Krusen
- 11 00-12 00 The Surgical Management of Esophageal Diverticulum
W Wayne Babcock and Chevalier Jackson

**C 3 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

X-Ray Museum, 6th Floor, Medical School Building

(Capacity, 50)

- 9 00-10 00 Hodgkins Disease
Clinical Aspects
Barton R Young
Radiology
W Edward Chamberlain
Pathology
Frank W Konzelmann

Thursday, May 2, 1935 (Continued)

- 10 00-10 30 Diseases of the Breast
W Emory Burnett
- 10 30-11 00 The Diagnosis of Malignant Disease with a Discussion of the Needle
Biopsy
Frank W Konzelmann and Barton R Young
-

**C 4 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Medical School Building, Room 502

(Capacity, 50)

- 11 00-12 00 The Nature and Clinical Applications of Bacteriophage Therapy
John A Kolmer
-

**C 5 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Outpatient Department, 2d Floor, Medical School Building

(Capacity, 20)

- 11 00-12 00 Demonstration of Retinal Changes in Medical and Neurological Con-
ditions by Means of the Multiocular Ophthalmoscope
Walter I Lillie and Glen G Gibson
-

**C 6 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

(Unlimited—No Tickets Required)

- 11 00-12 00 Demonstrations and Exhibits in Various Departments of the Hospital
and Medical School—Special Hospital Program will be available
-

D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Medical Clinic

(Capacity, 175)

- 9 00- 9 45 Syphilitic Heart Disease
John H Musser, New Orleans, La
- 9 45-10 30 Clinic on Peripheral Vascular Disease with Demonstration of Suction
and Pressure Apparatus
Lewis H Hitzrot
- 10 30-11 15 Clinic on Pulmonary Cases
Simon S Leopold

Thursday, May 2, 1935 (Continued)

- 11 15-11 30 The Results of Treatment in a Case of Addison's Disease
Henry U Hopkins
- 11 30-12 00 Clinic on Diabetic Cases
Francis D W Lukens

D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(34th and Spruce Streets)

Agnew Clinic

(Capacity, 225)

- 9 00- 9 30 Small Intestinal Intubation Its Value in the Study of Drug Actions
William Osler Abbott
- 9 30-10 30 Diagnosis and Treatment of Hypophyseal and Parahypophyseal Lesions
Charles H Frazier
- 10 30-11 30 Clinic on Gall Bladder Disease Correlation of Clinical Biliary Drainage and Cholecystographic Observations
T Grier Miller and E P Pendergrass
- 11 30-12 00 Clinic on Cardiac Cases
Charles C Wolferth

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a

- 9 00-10 30 Ward B
Edward Rose

D 3b

- 9 00-10 30 Ward D
Richard A Keen

D 3c

- 9 00-10 30 Pepper Ward
Isaac Stair, Jr

*Three above groups will alternate for the three following
sets of demonstrations*

Demonstrations in Maloney Clinic

- 10 30-11 00 8th Floor
Relation between Adrenals, Pituitary Body and Diabetes Mellitus
C N H Long and Staff
- 6th Floor, Department of Biophysics
Use of Short Wave Diathermy in Internal Medicine
D W Bronk and J P Herbey
- 3d Floor, Gastro-intestinal Department
Clinical Studies of Small Intestine
T Grier Miller and Staff

Thursday, May 2, 1935 (Continued)

- 11 00-11 30 Room 218
Immunity in Diabetes
Russell Richardson
- Room 709
Complement Fixation in Amoebiasis Nature of Test, Value in Acute and Chronic States, Value of Cultural, Wet Smear and Complement Fixation Methods
James S Forrester
- Room 709
New Method for Discovery of Sickle Cells in the Blood Method to Discover the Trait that Develops Sickle Cells, Method for Permanent Films, Some Clinical Data
James S P Beck
- Room 701
Colorimetric Readings by the Method of Optical Filters (Photronic Cells) Determination of Hemoglobin, Blood Sugar, Phosphates, etc, New Procedure for the Measurement of Serum Volume
F William Sunderman
- 11 30-12 15 Room 311, Robinette Foundation
Demonstration of the Use of Chest Leads in Electrocardiography
This demonstration will be of interest only to those with some knowledge of Clinical Electrocardiography
- Room 801
Demonstration of the Enzyme Accelerating the Up-take of CO_2 by the Blood
W C Stadie
- 5th Floor
Inspection of Department of Physiotherapy Discussion of various procedures
Josef B Nylin

D 4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL
BUILDING

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

- 9 00- 9 15 The Absorption of Sodium Tetraiodophenolphthalein from the Normal and Damaged Gall Bladder
Julian Johnson
- 9 15- 9 30 Measurement of Spinal Shock
G P McCouch, Joseph Hughes, W J Snape and W B Stewart
- 9 30- 9 45 The Effect of Oxygen in the Prevention of Liver Necrosis Induced by Volatile Anaesthetics
S Goldschmidt, I S Ravdin and Baldern Lucke
- 9 45-10 00 The Bile in Biliary Tract Disease
I S Ravdin, C G Johnson and C Riegel
- 10 00-10 20 The Emptying Time of the Stomach of the Dog before and after Gastric Operations
C G Johnson, I S Ravdin and E P Pendergrass
- 10 20-12 00 (a) Demonstrations in the Department of Physiology

Thursday, May 2, 1935 (Continued)

Room 126

- (1) Secretion of the Liver as Indicated by Dyes
R Hober

Room 34

- (2) Penetration of O₂ into the Skin in Man
S Goldschmidt and Bartgis McGlone

Room 136

- (3) Optical Method for more Accurate Estimation of Systolic, Diastolic and Dicrotic Wave Pressures in Man
H C Bazett and Louis B Laplace
- (b) Demonstrations in the Department of Research Surgery
- (1) Small Intestinal Fistulae
 - (2) Biliary Tract Fistulae
 - (3) Subcutaneous Kidney

There will also be demonstrations open to inspection from 9 00 to 12 00 in the Departments of Pathology, Bacteriology and Research Surgery

E 1

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Amphitheatre

(Capacity, 100)

- 9 00- 9 30 Medical Affections of the Biliary System
Frank Weigand
- 9 30-10 00 Cirrhosis of the Liver Correlation of Experimental and Clinical Findings
Jesse L Bollman, Rochester, Minn
- 10 00-10 30 The Indications for and Surgical Treatment of Biliary Tract Affections
George P Muller and Gilson Colby Engel
- 10 30-11 00 The Diagnosis and Medical Management of Peptic Ulcer
Daniel B Pierson, Jr
- 11 00-11 30 Bleeding Ulcer
James H Sterner
- 11 30-12 00 Surgical Types of Ulcer and their Treatment
Damon B Pfeiffer

E 2

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Research Institute

(Capacity, 50)

- 9 00- 9 30 Specimens and Discussion of Retroperitoneal Tumors
Clark E Brown
- 9 30-10 00 The Issues at Stake in the Grading of Tumors
Stanley P Reimann

Thursday, May 2, 1935 (Continued)

- 10 00-10 30 The Metastases of Carcinoma of the Stomach, with Especial Reference
to Krukenberg's Tumor
Clark E Brown
- 10 30-11 00 High Spots in Sulphur Metabolism
Grace Medes
- 11 00-11 30 The Toxicity of Certain Explosives Used in Industry
Clark E Brown
- 11 30-12 00 Choice of Media for Illustrating Medical Papers
Mrs Wm B McNett
-

E 3

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)
Men's Medical Ward, Second Floor
(Capacity, 15)

- 11 00-12 00 Ward Rounds
Frederick L Hartmann
-

F HAHNEMANN MEDICAL COLLEGE AND HOSPITAL
(Broad Street above Race)
Elkins Amphitheatre, 3d Floor
(Capacity, 200)

- 9 00- 9 30 Neurological Clinic
Edwin A Steinhilber
- 9 30-10 15 Hypertensive Cardiovascular Disease
G Harlan Wells
- 10 15-10 45 Hypothyroidism
Roger I Lee, Boston, Mass
- 10 45-11 15 Modern Treatment of Syphilis Illustrated by Selected Cases
C Walter Clarke, New York, N Y
- 11 15-12 00 Clinicopathological Conference
Grant O Favorite
-

G 1

PHILADELPHIA GENERAL HOSPITAL
(34th Street below Pine)
Clinical Amphitheatre
(Capacity, 250)

- 9 00- 9 30 Unilateral Non-tuberculous Bronchopneumonia of Long Duration
David Riesman
- 9 30-10 30 Syphilitic Heart Disease
(a) Prevailing Status
(b) Musical Murmurs
(c) Syphilitic Myocarditis
(d) Syphilitic Pericarditis
Thomas M McMillan, Samuel Bellet and Benjamin Gouley

Thursday, May 2, 1935 (Continued)

- 10 30-11 00 Intestinal Tuberculosis
Russell S Boles and J Gershon Cohen
- 11 00-11 30 Closed Pneumolysis Supplementary to Artificial Pneumothorax in Pulmonary Tuberculosis
George Willauer and David A Cooper
- 11 30-12 00 Factors Concerned in the Variations in Tolerance in Digitalis
Samuel Bellet
-

G 2

PHILADELPHIA GENERAL HOSPITAL

(34th Street below Pine)

Medical Section Building

(Capacity, 15)

- 9 00-10 00 Wind Walk
Thomas Klein
-

H 1

PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

Symposium on Diabetes

- 9 00-10 00 Clinic on Diabetes
Elliott P Joslin, Boston, Mass
- 10 00-10 20 Insulin Sensitivity
Merle M Miller
- 10 20-10 40 Allergic Manifestation of Epidermophytosis in Diabetes
Herbert T Kelly
- 10 40-11 00 Diabetes in Pregnancy
Ford A Miller
- 11 00-11 20 Dental Care of the Diabetic
James Aiguer, D D S
- 11 20-12 00 Simplified Diet Calculation for the Diabetic
Joseph T Beardwood, Jr, and Henrietta Pribnow
-

H 2

PRESBYTERIAN HOSPITAL

(39th Street and Powelton Avenue)

Ladies' Aid Room

(Capacity, 65)

- 9 00- 9 30 Treatment of Empyema
Henry P Brown and Orville King
- 9 30-10 00 Huge Suprarenal Tumor
George M Laws
- 10 00-10 30 Nephroptosis
Joseph C Birdsall

Thursday, May 2, 1935 (Continued)**10 30-12 00 Clinical-Pathological Conference**

Renal Calculi

Bilateral Reduplication of Kidneys

Congenital Megalo-ureter

Renal Tuberculosis

Teratoma Testis

Joseph C Birdsall, Francis Harrison and Kenneth E Fowler

H 3**PRESBYTERIAN HOSPITAL****(39th Street and Powelton Avenue)****Medical Ward****(Capacity, 15)****9 30-10 30 Ward Rounds**

George C Griffith

At 10 30 those making ward rounds may join the Clinical Pathological Conference in the Ladies' Aid Room

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL**(111 North 49th Street)****Auditorium****(Capacity, 250)****9 00- 9 20 Introduction**

Edward A Strecker

9 20- 9 40 Medical Aspect of the Neuroses

Lauren H Smith

9 40-10 00 Psychoanalytic-Medical Relationships

Kenneth E Appel

10 00-10 20 Physiological Factors in Psychiatric Research

Harold D Palmer

10 20-10 40 The Response of the Spinal Cord to Two Stimuli

Joseph Hughes

10 40-11 00 Post-Encephalitic Behavior Disorders

Earl D Bond

11 00-12 00 Historical Exhibit (Library of the Parent's Council) Books and

Curiosa Relating to Psychiatry

Clifford B Farr

Inspection of the Institute, Laboratories and Franklin School

K 1**JEFFERSON HOSPITAL****(10th and Sansom Streets)****Clinical Amphitheatre****(1020 Sansom Street)****(Capacity, 250)****9 00- 9 40 Diathermy Versus Vaccinal Therapy in Chorea**

Edward L Bauer

9 40-10 00 Hormonal Studies in Twins

Aaron Capper

Thursday, May 2, 1935 (Continued)

- 10 00-11 00 Nephrolithiasis
 Symptoms and Diagnosis
 Willard H Kinney
 Treatment
 Thomas C Stellwagen
- 11 00-11 30 Digitalis Therapy
 Ross V Patterson
- 11 30-12 00 Variations in Symptomatology and Physical Signs in Acute Coronary
 Thrombosis
 Henry K Mohler
-

K 2

JEFFERSON HOSPITAL
(10th and Sansom Streets)Curtis Clinic
(1015 Walnut Street)

Auditorium, 12th Floor

(Capacity, 170)

- 9 00- 9 20 Infection in Gall Bladder Disease
 Guy M Nelson
- 9 20- 9 40 Surgical Treatment of Pulmonary Tuberculosis
 George Willauer
- 9 40-10 00 The Male Sex Hormone
 James McCahey
- 10 00-10 15 Diagnosis of Hay Fever
 J Alexander Clarke, Jr
- 10 15-10 30 Routine Management of Asthma
 J Alexander Clarke, Jr
- 10 30-10 45 Treatment of Laryngeal Tuberculosis
 Robert M Lukens
- 10 45-11 00 Recent Advances in Medical Treatment of Pulmonary Tuberculosis
 Burgess L Gordon
- 11 00-11 15 Oxygen Therapy in Medicine
 Robert B Nye
- 11 15-11 30 Discussion and Presentation of Cases of Essential Hypertension
 Reynold S Griffith
- 11 30-12 00 A Tumor Clinic Presentation of Neoplasms of Gastro-intestinal Tract
 Edward J Klopp, David W Krumer, Willis F Manges, William
 Newcomet, Bruce L Fleming and George E Marcl
-

K 3

JEFFERSON MEDICAL COLLEGE
(1025 Walnut Street)

Auditorium

(Capacity, 75)

- 9 00-10 00 Clinicopathological Conference
 S A Loewenberg and Virgil H Moon

Thursday, May 2, 1935 (Continued)

- 10 00-10 30 Renal Tuberculosis Study and Diagnosis, Pathological and Bacteriological Phase
Carl J Bucher
- 10 30-11 00 Urological and Roentgen Ray Phase (Lantern Slides)
Theodore R Fetter
- 11 00-12 00 Recent Advances in Treatment of Diseases of the Skin
Frank C Knowles and Edward F Corson
-

K 4

JEFFERSON HOSPITAL

(10th and Sansom Streets)

Second Floor Medical

(Capacity, 15)

- 11 00-12 00 Ward Walk
Fred J Kalteyer
-

L 1

PENNSYLVANIA HOSPITAL

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Hospital Chapel

(Capacity, 200)

William D Stroud presiding

Cardiovascular Symposium

- 9 00- 9 45 The Electrocardiogram as an Aid to the Diagnosis and Prognosis of
Acute Coronary Occlusion
Joseph B Vander Veer
- 9 45-10 45 Acute Pulmonary Edema in Heart Disease
Paul D White, Boston, Mass
- 10 45-11 30 Coronary Disease, Including Angina Pectoris
William D Stroud
- 11 30-12 00 X-Ray Findings in Calcification of the Heart Valves and Pericardium
Paul A Bishop
- 9 00- 1 00 P M The Library of the Pennsylvania Hospital, which is the first
Medical Library of this country, will be open from 9 00 until
1 00 daily Dr Francis R Packard is in charge of arranging
this exhibit

Thursday, May 2, 1935 (Continued)

L 2

PENNSYLVANIA HOSPITAL

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Surgical Clinic

(Capacity, 200)

Thomas McCrae presiding

Symposium on New Growths of the Lung

- 9 00- 9 45 The Diagnosis of New Growths of the Lung from the Bronchoscopic Standpoint
Louis H. Clerf
- 9 45-10 30 The Diagnosis and Treatment of New Growths of the Lung from the Roentgenographic Standpoint
Paul A. Bishop
- 10 30-11 15 The Diagnosis and Treatment of New Growths of the Lung from the Standpoint of the Internist
Robert P. Regester
- 11 15-12 00 The Surgical Treatment of New Growths of the Lung
John B. Flick
-

L 3

PENNSYLVANIA HOSPITAL

(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Ward Rounds

1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

- 9 00-10 00 Wards 3 and 4
David L. Farley and Associates

L 3b

- 9 00-10 00 Wards 1 and 4
Thomas McCrae, Robert P. Regester and Associates
Two above groups will consolidate for balance of program

Ayer Clinical Laboratory

(Capacity, 24)

- 10 00-11 00 Clinicopathological Conference
John T. Bauer

Outpatient Department

- 11 00-11 30 Adult Heart Clinic Demonstration
Thomas M. McMillan
- 11 30-12 00 The Administration of a Hospital Outpatient Department
Samuel Bradbury

Friday, May 3, 1935

A 1

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Catherwood House
(Main Entrance, Bainbridge Street below 18th)

(Capacity, 125)

- 9 00-10 00 Artificial Pneumothorax in Tuberculosis in Children
F Maurice McPhedran
- 10 00-11 00 Enuresis as a Psychiatric Problem
Frederick H Allen
- 11 00-12 00 Urological Lesions in Upper Urinary Tract in Children
Albert E Bothe
-

A 2

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Ward Walk
(Entrance, Bainbridge Street below 18th)

(Capacity, 10)

- 9 00-10 20 Ward Walk
John C Gittings
-

A 3

CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Assembly Room, Department of Prevention of Disease
(Entrance, 1721 Fitzwater Street)

Demonstrations

(Capacity, 75)

- 10 30-11 00 Application of the Refractometer to Clinical Material
Horace L Hodes
- 11 00-11 30 Congenital Pulmonary Malformations
Irving J Wolman
- 11 30-12 00 Demonstration of Technique of Virus Culture
Arthur D Waltz and Alice Chenoweth
-

B 1 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 150)

- 9 00- 9 40 Clinic on Gastric Ulcer
Sara Jordan, Boston, Mass

Friday, May 3, 1935 (Continued)

- 9 40-10 20 Puzzling Types of Indigestion
Walter Alvarez, Rochester, Minn
- 10 20-11 00 Gastro-enterological Conference
H L Bockus, W Estell Lee, Karl Kornblum and Eugene Case
- 11 00-11 15 Experience with Spinal Anaesthesia in Gastro-intestinal and Intra-abdominal Surgery
W Estell Lee and Orville King
- 11 15-11 30 Roentgen Diagnosis of "Milk of Calcium" Bile
Karl Kornblum
- 11 30-11 50 Abdominal Symptomatology in Diabetic Acidosis
Joseph T Beardwood, Jr
- 11 50-12 00 A Case of Lead Poisoning of Unusual Origin
John H Willard
-

**B 2 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

Center Lecture Room

(Capacity, 75)

- 9 00-9 20 Presentation of a Family with Hemophilia
H Leon Jameson
- 9 20-10 10 The Clinical Significance of Venous Pressure Estimation
George C Griffith and J Roderick Kitchell
- 10 10-11 00 Factors Influencing Sedimentation Test
Fred Boerner
- 11 00-12 00 Esophagosopic Observations in Diseases of the Esophagus
Gabriel Tucker
-

**B 3 GRADUATE HOSPITAL OF THE UNIVERSITY OF
PENNSYLVANIA**
(19th and Lombard Streets)

Assemble at Private Admissions' Desk**Demonstrations and Ward Clinics**

(Capacity, 15)

- 9 00- 9 45 A New Test for the Phagocytic Power of Whole Blood
Fred Boerner and Stuart Mudd
- 9 45-10 30 Presentation of Material from the Chest Clinic
Richard T Ellison
- 10 30-11 15 Ward Rounds
B J Appers
- 11 15-12 00 Bedside Observations in Cardiovascular Disease
(a) Determination of Heart Size
(b) Determination of Arteriosclerosis
Hugh Miller

Friday, May 3, 1935 (Continued)

**C1 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Auditorium, 3d Floor, Medical Building

(Capacity, 250)

- 9 00- 9 15 An Analysis of 100 Cases of Hemoptysis from the Bronchoscopic
Clinic
N M Levin
- 9 15- 9 45 Hiatal Hernia of the Stomach and Congenital Short Esophagus
C L Jackson and Albert K Merchant
- 9 45-10 00 A Method of Directly Recording Bronchial Contractions
M P Ellis and Alfred E Livingston
- 10 00-10 30 Gastroscoy with Special Reference to the Flexible Gastroscope
C L Jackson and W A Swalm
- 10 30-11 00 The Suigical Treatment of Pulmonary Suppuration
W Emory Burnett
- 11 00-11 30 Bronchoscopy in Acute and Chronic Infections of the Trachea and
Bronchi
Chevalier Jackson
- 11 30-12 00 The Role of Oral Spirochetes and Associated Anaerobes in Pyorrhea
and Pulmonary Abscess (Motion Picture Demonstration)
Arthur Q Penta
-

**C2 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

Surgical Amphitheatre, 3d Floor, Hospital

(Capacity, 100)

- 9 00- 9 15 Studies on Pituitary Extracts
Edward Larson
- 9 15- 9 30 Pituitary Basophilism
Michael G Wohl and Barton R Young
- 9 30-10 00 Agranulocytosis and the Leukemias
W Edward Chamberlain and Louis Soloff
- 10 00-11 00 Etiology and Management of Various Forms of Anemia
Maurice B Strauss, Boston, Mass
-

**C3 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

X-Ray Museum, 6th Floor, Medical School Building

(Capacity, 50)

- 9 00- 9 30 The Treatment of Cardiovascular Syphilis
Jacques Guequierre
- 9 30- 9 45 Constriction of the Aorta
Morris Kleinbart

Friday, May 3, 1935 (Continued)

- 9 45-10 15 The Heart and Athletics
Hugo Roesler
10 15-11 00 Low Back Pain
W Edward Chamberlain and John Royal Moore
-

**C 4 TEMPLE UNIVERSITY MEDICAL SCHOOL AND
HOSPITAL**

(3400 North Broad Street)

(Unlimited—No Tickets Required)

- 11 00-12 00 Demonstrations and Exhibits in Various Departments of the Hospital
and Medical School—Special Hospital Program will be available
-

D 1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Medical Clinic

(Capacity, 175)

- 9 00- 9 30 The Treatment of the Attack in Paroxysmal Tachycardia and Other
Clinical Uses of Derivatives of Choline Case Demonstrations
Isaac Starr, Jr
9 30-10 00 Clinic on Agnucloctic Angina
Thomas Fitz-Hugh, Jr
10 00-10 45 Clinical Allergy
Richard A Kern
10 45-11 30 Clinic on the Diagnosis and Treatment of Hypothyroid States
Edward Rose
11 30-12 00 Clinicopathological Conference
Baldern Lucke and Medical Staff
-

D 2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(34th and Spruce Streets)

Agnew Clinic

(Capacity, 225)

- 9 00-10 00 Clinic on Biliary Tract Disease
I S Raydin and Associates
10 00-10 30 The Functions and Disorders of the Sympathetic Nervous System
Detlev W Bronk
10 30-10 45 The Carotid Sinus Reflex in Patients with Hypertension
George Gammon
10 45-11 15 Diagnosis and Treatment of the Common Dermatoses
Vaughn C Garner
11 15-12 00 Clinic on Ureteral Obstruction
Alexander Randall

Friday, May 3, 1935 (Continued)

D 3 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA
(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

D 3a9 00-10 30 Ward B
James E Cottrell**D 3b**9 00-10 30 Ward D
Charles C Wolferth**D 3c**9 00-10 30 Pepper Ward
Leon H Collins, Jr*Three above groups will alternate for the three following sets of demonstrations*

Demonstrations in Maloney Clinic

10 30-11 00 8th Floor

Relation between Adrenals Pituitary Body and Diabetes Mellitus

C N H Long and Staff

6th Floor, Department of Biophysics

Use of Short Wave Diathermy in Internal Medicine

Detlev W Bronk and J P Herby

3d Floor, Gastro-intestinal Department

Clinical Studies of Small Intestine

T Grier Miller and Staff

11 00-11 30 Room 218

Immunity in Diabetes

Russell Richardson

Room 709

Complement Fixation in Amoebiasis Nature of Test, Value in Acute and Chronic States, Value of Cultural, Wet Smear and Complement Fixation Methods

James S Forrester

Room 709

New Method for Discovery of Sickle Cells in the Blood Method to Discover the Trait that Develops Sickle Cells, Method for Permanent Films, Some Clinical Data

James S P Beck

Room 701

Colorimetric Readings by the Method of Optical Filters (Photronic Cells) Determination of Hemoglobin, Blood Sugar, Phosphates, etc, New Procedure for the Measurement of Serum Volume

F William Sunderman

11 30-12 15 Room 311, Robinette Foundation

Demonstration of of Chest Leads in T

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Friday, May 3, 1935 (Continued)

- 9 45-10 15 The Heart and Athletics
Hugo Roesler
10 15-11 00 Low Back Pain
W Edward Chamberlain and John Royal Moore
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Friday, May 3, 1935 (Continued)

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(36th and Spruce Streets)

Bedside Conferences

(Capacity, 15 each)

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James E Cottiell

D 3b

9 00-10 30 Ward D
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Colorimetric Readings by the Method of Optical Filters (Photronic Cells) Determination of Hemoglobin, Blood Sugar, Phosphates, etc, New Procedure for the Measurement of Serum Volume

F William Sunderman

11 30-12 15 Room 311, Robinette Foundation

Demonstration of the Use of Chest Leads in Electrocardiography
This demonstration will be of interest only to those with some knowledge of Clinical Electrocardiography

Friday, May 3, 1935 (Continued)

Room 801

Demonstration of the Enzyme Accelerating the Up-take of CO_2 by the Blood

W C Stadie

5th Floor

Inspection of Department of Physiotherapy Discussion of various procedures

Josef B Nylin

D 4 UNIVERSITY OF PENNSYLVANIA MEDICAL SCHOOL
BUILDING

(36th Street and Hamilton Walk)

Lecture Room D

(Capacity, 100)

- 9 00- 9 30 Possibilities of Use of Serum from Human Sources (a) Pooled Normal Adult, (b) Convalescent, (c) From Hyperimmunized Donors, in Prevention and Treatment of Infectious Disease
Stuart Mudd
- 9 30-10 00 Recent Studies on Urine Formation
A N Richards
- 10 00-10 30 Carotid Sinus Reflexes Their Role in the Regulation of Respiration and in the Action of Certain Respiratory Stimulants
Carl F Schmidt
- 10 30-12 00 (a) Demonstrations in the Department of Bacteriology Room 214
(1) New Method of Preservation of Serum
Earl W Flordorf
(2) An Improved Phagocytic Method as a Measure of the Virulence of an Organism and of the Efficacy of Therapeutic Sera
Fred Boerner and Stuart Mudd
(3) Eagle Test for Syphilis
Harry Eagle
(4) Rough Smooth and Filterable Variants of the Diphtheria Bacillus
Harry E Morton
(b) Demonstrations in the Department of Pharmacology

Room 164

- (1) Carotid Sinus Reflexes Caused by Physical and Chemical Agents
H A Royster, Jr, W B Test and Carl F Schmidt
(2) Demonstrations of Methods Used in the Direct Study of Glomerulus and Tubule in the Amphibian Kidney
Arthur M Walker, Hugh Montgomery and J P Hendrix

There will also be demonstrations open to inspection from 9 00 to 12 00 in the Departments of Pathology, Bacteriology and Research Surgery

Friday, May 3, 1935 (Continued)

E 1

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Amphitheatre

(Capacity, 100)

- 9 00- 9 30 Choice of Cases for Various Types of Treatment in Pulmonary Tuberculosis
Francis M Pottenger, Monrovia, Calif
- 9 30-10 00 Surgical Treatment of Tuberculosis
George P Muller
- 10 00-10 30 Agranulocytosis
Henry Jackson, Boston, Mass
- 10 30-11 00 Diagnosis and Treatment of Head Trauma
Clarence A Patten
- 11 00-11 30 Habitual Hyperthermia
Hobart A Reimann, Minneapolis, Minn
- 11 30-12 00 Hematuria
William H Mackinney
-

E 2

LANKENAU HOSPITAL
(Corinthian and Girard Avenues)

Men's Medical Ward, Second Floor

(Capacity, 15)

- 11 00-12 00 Ward Rounds
Edward L Bortz
-

F HAHNEMANN MEDICAL COLLEGE AND HOSPITAL
(Broad Street above Race)

Elkins Amphitheatre, 3d Floor

(Capacity, 200)

- 9 00- 9 30 Diseases of the Hemopoietic System in Children
C S Raue
- 9 30-10 00 Juvenile Diabetes Mellitus
William R Williams
- 10 00-10 30 Pernicious Anemia and Intravenous Liver Extract
Dunne W Kirby
- 10 30-11 00 Chest Pain
George D Geckeler
- 11 00-11 30 Atypical Leukemias
Ernest B Bradley, Lexington, Ky
- 11 30-12 00 Clinicopathological Conference (Pediatric)
Carl C Fischer and Russell Fischer

Friday, May 3, 1935 (Continued)

G 1**PHILADELPHIA GENERAL HOSPITAL**

(34th Street below Pine)

Auditorium

(Capacity, 200)

- 9 00- 9 45 Pericarditis
 (1) Observations on the Electrocardiographic Changes in Acute Variety
 (2) *a*—Acute and Tuberculous Varieties—Signs, Symptoms and X-Ray Findings
 b—Differentiation from Rheumatic Type
 (3) *a*—Basal Constricting Pericarditis (Pulmonary Artery)
 b—Evidences to Show that the Tuberculous Variety Does Recover and Become Adhesive
 Thomas M. McMillan and Benjamin Gouley
- 9 45-10 05 The Ability of the Heart to Recover Completely from Extreme Dilatation
 Louis B. Laplace
- 10 05-10 35 A Comparative Study of Venous, Intraspinal and Arterial Pressures with Especial Reference to Failure of the Right Heart
 Harold F. Robertson
- 10 35-11 05 Aneurysms of the Sinuses of Valsalva and Studies of the Interventricular Septum
 Benjamin Robinson
- 11 05-11 25 Low Blood Urea
 Frank Levy
- 11 25-12 00 Some Unusual Phases of Rheumatic Fever
 Robert G. Lorrev and R. P. Custer

G 2**PHILADELPHIA GENERAL HOSPITAL**

(34th Street below Pine)

Clinical Amphitheatre

(Capacity, 250)

- 9 00- 9 50 Arterial Hypertension
 Leonard G. Rowntree
- 9 50-10 05 Fever Therapy
 (*a*) Gonorrheal Arthritis
 (*b*) Chorea
 Ferdinand Fetter
- 10 05-10 35 The Clinical Application of the Various Methods of Investigating the Circulation of the Extremities
 David W. Kramer
- 10 35-11 35 The Treatment of Diabetic Lesions of the Feet, with Especial Reference to Non-surgical Management
 Edward S. Dillon and Lewis H. Hitzrot
- 11 35-11 45 Studies in Febrile Albuminuria
 John W. Welty
- 11 45-12 00 Weil's Disease
 Kenneth L. Reynolds and R. E. Otten

Friday, May 3, 1935 (Continued)

G 3 PHILADELPHIA GENERAL HOSPITAL (34th Street below Pine)

Medical Section Building

(Capacity, 15)

9 00-10 00 Ward Walk
Henry D Jump

H 1 PRESBYTERIAN HOSPITAL (39th Street and Powelton Avenue)

Gymnasium

(Capacity, 150)

9 00- 9 50 Diseases of the Adrenals
David P Barr, St Louis, Mo
9 50-10 20 Treatment of the Naevi
William S Newcomet
10 20-11 00 Relation of Posture to Diagnosis
William Bates and J C Howell
11 00-12 00 Medical Clinic
John B Youmans, Nashville, Tenn

H 2 PRESBYTERIAN HOSPITAL (39th Street and Powelton Avenue)

Ladies' Aid Room

(Capacity, 65)

9 00- 9 30 Orthopedic Care of Arthritis
T E Orr
9 30-10 30 Lumbar Ganglionectomy in Arthritis
F A Bothe
10 30-12 00 Clinical-Pathological Conference
Multiple Myeloma
Paul North
Fibroblastoma of Frontal Lobe
W B Cadwalader
Congenital Tuberculosis
Charles A Fife
Erythroblastosis Fetalis
John P Scott

H 3 PRESBYTERIAN HOSPITAL (39th Street and Powelton Avenue)

Children's Ward

(Capacity 15)

9 30-10 30 Ward Rounds
John P Scott

At 10 30 those making ward rounds may join the Clinical-Pathological Conference in the Ladies' Aid Room

Friday, May 3, 1935 (Continued)

J INSTITUTE OF THE PENNSYLVANIA HOSPITAL
(111 North 49th Street)

No Program On Friday

K JEFFERSON HOSPITAL
(10th and Sansom Streets)

Clinical Amphitheatre
(1020 Sansom Street)

(Capacity, 250)

- 9 00-10 00 The Diagnosis and Treatment of Certain Diseases of the Esophagus
Roentgen Ray
Willis F Manges
Esophagoscopy
Louis H Clerf
Surgical
Thomas A Shallow
- 10 00-11 00 Brain Tumor
William Duane, Jr, Benjamin Weiss and Michael A Burns
- 11 00-11 20 Physiology of the Stomach in Relation to Ulcer
J Earl Thomas
- 11 20-11 40 Surgical Aspect
Edward J Klopp
- 11 40-12 00 Medical Aspect and Gastric Photography
Martin E Rehfuess

L 1 PENNSYLVANIA HOSPITAL
(Entrance on 8th Street,
halfway between Spruce and Pine Streets)

Hospital Chapel

(Capacity, 200)

F William Sunderman presiding

Symposium on Diabetes and Metabolic Abnormalities

- 9 00- 9 45 Diabetic Arteriosclerosis
Edward S Dillon
- 9 45-10 30 Diabetic Acidosis with Especial Reference to Therapy
F William Sunderman
- 10 30-11 15 Heart Muscle Efficiency in Metabolic Disorders
Jonathan C Meakins, Montreal, Que
- 11 15-12 00 Interpretation of Renal Tests
Joseph M Hayman, Jr, Cleveland, Ohio
- 9 00- 1 00 P M The Library of the Pennsylvania Hospital, which is the first
Medical Library of this country, will be open from 9 00 until
1 00 daily Dr Francis R Pickard is in charge of arranging
this exhibit

Friday, May 3, 1935 (Continued)

L 2**PENNSYLVANIA HOSPITAL**(Entrance on 8th Street,
halfway between Spruce and Pine Streets)**Surgical Clinic**

(Capacity, 200)

Thomas McCrae presiding

- 9 00- 9 45 Duodenal Extract in the Treatment of Diabetes Mellitus
Garfield G Duncan
- 9 45-10 30 Clinic on the Acute Abdominal Syndrome and Infections in Diabetes
Edward H Mason, Montreal, Que
- 10 30-11 15 Clinic on Hypothyroidism
Roger I Lee, Boston, Mass
- 11 15-12 00 Medical Clinic
Thomas McCrae
-

L 3**PENNSYLVANIA HOSPITAL**(Entrance on 8th Street,
halfway between Spruce and Pine Streets)**Ward Rounds**

1st and 2nd Floors, Pine Street Building

(Capacity, 12 each)

L 3a

- 9 00-10 00 Wards 3 and 4
David L Farley and Associates

L 3b

- 9 00-10 00 Wards 1 and 4
Thomas McCrae, Robert P Regester and Associates

*Two above groups will consolidate for balance of program***Ayer Clinical Laboratory**

(Capacity, 24)

- 10 00-11 00 Clinicopathological Conference
John T Bauer
Discussion, opened by John R Paul, New Haven, Conn

Outpatient Department

- 11 00-11 30 Allergy Clinic Demonstration
James S McLaughlin
- 11 30-12 00 The Administration of a Hospital Outpatient Department
Samuel Bradbury

MINUTES OF THE MEETING OF THE BOARD OF REGENTS, PHILADELPHIA, DECEMBER 16, 1934 (*Continued*)

Upon motion by Dr Barr, seconded and regularly carried, it was *Resolved*,

(1) That the name of the John Phillips Memorial Prize Committee be changed to the Committee on Fellowships and Awards

(2) That a die be cast from a design herewith presented by the Committee for a medal to be awarded "For Achievement in Internal Medicine"

(3) That in order to make the series of Phillips medalists complete, medals be given to Dr Avery and to Dr Castle, the former recipients of the prize

(4) That the John Phillips Memorial Medal of the American College of Physicians be awarded in 1935 to Professor Leo Loeb In making this recommendation the Committee has in mind the rich accomplishment of a life time devoted to researches in the medical sciences and particularly Professor Loeb's recent investigations which have greatly extended our knowledge of the action of that hormone of the anterior pituitary gland whose injection produces the main symptoms of Graves' disease in animals

During his approximately 40 years of active work Professor Loeb has contributed to many fields of general and experimental pathology His first researches in 1895 concerned the transplantation of pigmented skin This later developed into a study of the main factors underlying transplantations in general, and has more recently led to an analysis of organismal differentials and individuality in various life processes, including immunity

Early studies of wound healing led to researches on the mechanism of growth, tissue culture and tissue formation in general and to the production of experimental "amebocyte tissue," which served as a model and which aided in the analysis of ameboid movement, tissue stereotropism and other factors active in wound healing and inflammatory processes

These last investigations led to a study of the agglutinative processes underlying thrombosis and to the specific adaptations which exist between blood plasma and the factors accelerating and inhibiting coagulation of blood

At a very early stage Professor Loeb undertook investigations in the pathological physiology of tumors, which have been continued during his many years of work His well known pioneer researches on the transplantation of malignant tumors in animals made possible the study of heredity in tumors and the first quantitative determination of this factor

Investigations concerning the relationship between hereditary factors and internal secretions in the origin of tumors led to a study of the internal secretions in the ovary and of the mechanism underlying the sex cycle, to an analysis of the functions of the corpus luteum and of the factors underlying placenta formation and the development of experimental placentomata

In this connection Professor Loeb also studied the occurrence of far going parthenogenetic development of ova and of the formation of chorion epitheliomatous structures in the mammalian ovary and their relationship to the interpretation of certain tumors found in man

The investigations concerning the sexual cycle led to an analysis of certain hormones of the anterior pituitary and their significance for the ovary and the thyroid gland

While these have been the main lines of Professor Loeb's researches, he has also made important contributions on the analysis of the venom of *Heloderma*, upon certain factors underlying edema, on the urease occurring in amebocytes, the relations

between various cations and enzyme action and upon the intrauterine inoculation of microorganisms into the closed uterine cavity

Since 1929 Professor Loeb has published a long series of papers upon the effects of injection of the thyroid influencing hormone of the anterior hypophysis. Through these important studies on experimental animals dealing especially with the increased mitotic activity of the thyroid cells, changes in iodine content of the thyroid gland, elevations of basal metabolism, circulatory changes and exophthalmos, it has been made clear that the symptoms of Graves' disease may be reproduced in mammals by the injection of this hormone.

(5) That letters be sent to Professors of Medicine and of Pediatrics, and to members of the Board of Regents, requesting recommendations for candidates for the Research Fellowship of the American College of Physicians and that the form of recommendation be of the general type used by the National Research Council.

Dr Luther F. Warren reported for the Committee on Extension of Postgraduate Education in the absence of Dr F. M. Pottenger, Chairman. Dr Warren explained that the specific matter on which the Committee was requested to report was a resolution passed by the Board of Regents at one of its April 1934, meetings, providing an investigation of the advisability of, and formulation of plans for, the closer organization and greater cohesion of our members in their particular communities or States, such as is done by the American College of Surgeons through sectional meetings, with the object of carrying extension postgraduate medical educational facilities to physicians in more remote locations. The Committee presented the recommendation that the Board of Regents shall encourage the Governors of the several States to have local clinical meetings, with the object of stimulating the purpose of the College. The adoption of the report was moved and seconded.

In the discussion that ensued, the following matters were pointed out: (1) the Chairman of the Board of Governors would be requested to inform the several Governors of the action of the Board of Regents, (2) State Medical Societies are carrying on an enormous amount of sectional work, and the College should not duplicate their efforts, (3) such meetings, as recommended by the Committee, would promote greater comradeship among the Fellows in each district, and make the College a little more tangible to them, (4) the recommendation is very broad and there should be much latitude given to members in the method of conducting these meetings, (5) that the plan is presented purely as an experimental one, (6) that the College might officially assist through the Executive Offices and even by financial aid, where justified.

Dr Warren accepted an amendment to the resolution presented by Dr White, and by unanimous vote, it was

Resolved, that the Board of Regents shall encourage the Governors of the several States, singly or in regional cooperation, to have local clinical meetings, with the object of stimulating the purposes of this College.

Dr Charles F. Martin, Chairman of the Committee on Finance presented the following report:

"(1) Income and Expenses January 1, 1934, to November 30, 1934, with estimated income and expenses for the month of December 1934. (2) Budget Comparison, for expenditures and budget appropriations for 1934, (3) Cost Analyses for *ANNALS OF INTERNAL MEDICINE*, Volumes V, VI and VII, (4) Comparative Cost Analyses for the Annual Clinical Sessions, San Francisco, Montreal and Chicago (1932, 1933 and 1934).

"These statements have been prepared for you by the Executive Secretary. The feature of these reports is their prophetic accuracy. Added to this is the conscientious adherence to expenditures within the budgets.

"Your Committee has the honor to report a most satisfactory condition of the finances of the College during the past 11 months. The financial year terminates

December 31, so the time is not ripe for a complete detailed statement. The picture, however, is adequate. Features of interest in the report are (1) maintenance of annual dues in excess of all expectation, (2) increase in initiation fees, (3) increase in Life Membership Fees (Secretary stimulated interest), (4) profit from sale of securities, (5) profitable operation of *ANNALS*—printers and advertising, (6) total excess of income over expenditures for year \$16,000 00.

"Your Committee regards it as a pleasant duty to congratulate the Executive Secretary, the Treasurer, and administration generally, and to express their unqualified appreciation of the management of the finances of the College—all the more remarkable in view of general business conditions.

'*Investments* Your Committee believes in a more concrete designation of the funds of the College, and suggests

All moneys, securities and investments be included in the term, General Funds

Under this heading may be stipulated

- (1) Endowment Fund and any other restricted funds, which, with respect to capital, are not to be utilized for current expenses—though the interest may be added to the current account. This fund amounts to approximately \$54,000 00.
- (2) Free current or unrestricted funds, which may include the investment account, bank balances and any other cash or liquid assets. These total approximately \$70,000 00.

'A scrutiny of present securities has suggested to your Committee the need of some change in the nature of the investments, more especially the sale of some of the municipal bonds. In practically every instance this may be achieved with some profit.

'In consideration of further investments, your Committee asks the endorsement of the Board of Regents on the policy of investing some of the College moneys, not exceeding 15 per cent, in carefully selected stocks, as necessary protection versus possible inflation.

"It further recommends the purchase of some Canadian securities both bonds and stocks, the latter not to exceed a proportion of 15 per cent of the total Canadian investments.

"In conclusion, the Committee asks approval of the tentative budget of the Executive Secretary and the Treasurer for 1935 (in which income is estimated at \$68,000 00 and expenditures at \$52,125 00) until such time in April as the Board receives more detailed figures at its Annual Session.

Respectfully,

JAMES ALLEN MILLER

ROGER I. LEE

C. F. MARTIN, *Chairman*

On motion by Dr. Martin, seconded by Dr. Herrick, and regularly carried it was *Resolved*, that the report of the Committee on Finance be approved.

Dr. William D. Stroud, Treasurer, spoke briefly to the effect that the College should be much encouraged by the financial situation of its investments, the manner in which the funds are being collected and the careful way in which those in charge of expending funds have stayed within their budgets.

Dr. Maurice C. Pincoffs, Editor, and Chairman of the Committee on the *ANNALS OF INTERNAL MEDICINE*, reported that he had held no formal meeting of his Committee owing to the fact that local business in Baltimore had prevented his arriving in the City sufficiently in advance of the Regents' meeting. He said he had nothing in particular to report, other than such reactions as he receives, for the most part favorable to the publication policy for the journal, and occasional communications suggesting the advisability of adding more clinical articles. Bedside clinical articles

are the most difficult to obtain. There is a great field for someone who will write interestingly about clinical disease rather than the measurement of disease. The ANNALS has been running on a satisfactory basis, to expand the ANNALS to some additional fields is a matter open for discussion in the Board of Regents. Dr. Pincoffs expressed the desire to have suggestions and criticisms from the Board. The fact that the journal is carrying itself financially may make expansion feasible, such as the inauguration of some particular instructional feature or features.

On motion by Dr. James Alex. Miller, seconded by Dr. James B. Herrick, and regularly carried, it was

Resolved, that the Board of Regents express its tremendous satisfaction with the work of the Editor, and extend to him their congratulations and thanks.

Dr. James Alex. Miller, Chairman of the Committee on Public Relations, presented the following matters that had been referred to his Committee:

(1) "Twenty paragraphs on Cooperative Hospital Service" from the President of the Allegheny (Pa.) County Medical Society, with the suggestion that this body may be willing to give an opinion thereon.

Dr. Miller expressed the opinion that the College is not in a position to know of such local experiments, and that there is actually nothing to act on.

On motion by Dr. Miller, seconded by Dr. Pepper, and regularly carried, it was

Resolved, that the College acknowledge receipt of the material, express its appreciation and state that it is not in a position to express approval or disapproval of such local experiments.

(2) A communication from Dr. William Henry Walsh (Fellow), of Chicago, setting forth a plan by which the College might take an active part in an organized way in familiarizing itself with what is going on in the field of hospital practice and medical economics, and setting forth also a definite proposition for a council on professional service.

(3) A communication to Dr. James H. Means, suggesting that the College should take some definite stand on medical economic problems, citing the fact that three members of our Board of Regents are on the Medical Advisory Board of President Roosevelt's Committee on Economic Security.

Dr. Miller stated that the Medical Advisory Board, on which Dr. Walter L. Bierring (Regent), Dr. George Morris Piersol (Regent), Dr. James D. Bruce (Governor) and Dr. Stewart R. Roberts (Fellow) and himself (Officer) are among the members, had sat in conference with President Roosevelt on an interesting discussion and review of the present situation, in which some of the progress that has been made in Washington was laid before the Board.

Dr. Miller suggested that the Regents of the College consider if the College has any function in this situation. He reported that there is now very great likelihood of better reaction toward the matter of medical economics and that the American Medical Association has been requested and has accepted the responsibility of assisting in working out some solution to some of the economic problems. It was felt that the American Medical Association has adopted an interested and constructive attitude in this matter. The question has arisen as to what action the College should take, if any. The Committee on Public Relations felt that the College should do nothing that would embarrass in the least degree the new relations that have been established with the American Medical Association, and that any initiative on the part of the College should be in the direction of coordination and in harmony with their program.

The Committee voted to suggest to the Board of Regents the possibility of using the ANNALS OF INTERNAL MEDICINE as a medium of regular distribution or dissemination of knowledge about these economic problems, working up a definite number of articles on various selected subjects. These articles should not in any way commit the College to any policy, but be purely informative and educational, present-

ing the problem, stating what has been done in this and other countries and, in general, informing our members of the various features of the situation. The Committee has consulted with the Editor, Dr. Pincoffs, who is sympathetic to the idea. The College might think it worth while to ask other cooperation in this matter, to start with a preparatory explanation of what the object is and then to have an advisory committee to the Editor to collect the articles and publish them in a definite series. It is possible that after a year of education in this matter, the whole situation could be definitely crystallized in one or two outstanding papers on our clinical program for 1936.

Dr. Pincoffs, as Editor of the *ANNALS*, said that he considered the object well within the purpose of the journal, and that the *ANNALS* should not be merely another clinical journal, but that it should express some purposes of the College. Either the Committee on Public Relations, or an expanded committee, might be appointed to select and prepare the series of articles proposed.

Dr. Miller pointed out that no cost is necessary. The College could adopt a working arrangement, putting the responsibility on the Committee for informing the American Medical Association of our willingness to cooperate with their program, asking their suggestions and working in harmony with what they have in mind. This would be merely a courteous gesture, the College offering to them this facility.

After some further discussion concerning the recommendations of Dr. Walsh, on motion by Dr. Miller, seconded by Dr. Pincoffs, and regularly carried, it was

Resolved, that the Committee be authorized to express the appreciation of the College to Dr. William Henry Walsh for his tendered cooperation and to express the feeling that the Board of Regents do not consider the time ripe for the adoption of a Council on Professional Service and Administrative Practice by the College.

On motion by Dr. Miller, seconded and regularly carried, it was

Resolved, that the College adopt the recommendation of the Committee on Public Relations, that the Editor of the *ANNALS* prepare an editorial concerning the discussion by the Board of Regents on the problem of medical economics and further arrange to publish in the *ANNALS* a series of articles of a purely educational and instructive nature on this problem. Furthermore, that the Committee inform the American Medical Association of our plan and ask for suggestions in an effort to harmonize our work with what they have in mind, this being a courteous gesture on the part of the College and an effort to offer to them this facility of our organization. Furthermore, the Committee on Public Relations, for this specific purpose, may be augmented by the addition of such members as are deemed helpful.

President Meakins thereupon appointed Dr. Maurice C. Pincoffs as an additional member, pro tem, of the Public Relations Committee, with authorization to the Chairman, Dr. James Alex. Miller, to add, pro tem, such additional members as he may see fit.

President Meakins called upon Dr. Alfred Stengel, General Chairman of the Philadelphia Clinical Session, to report upon local arrangements.

Dr. Stengel reported that he had delayed making local arrangements for clinics, giving the local profession time to rest up and get organized after the recent meeting in Philadelphia of the Interstate Postgraduate Medical Association. He has now organized his committees, selected several hospitals in which clinics will be given, and selected a chairman for each hospital. These chairmen have been requested to indicate the facilities they have available in the way of lecture rooms, exhibits, etc. In the next few weeks the program of clinics and demonstrations will be well underway. A new feature of the meeting in Philadelphia will be two morning meetings in lecture rooms at the auditorium in addition to the regular clinics. Guests, possibly a few local members, will be invited to give purely clinical talks for those who may elect them instead of hospital clinics. Seats will be reserved for Fellows of the College, and the balance of the space thrown open for guests from the County Medical Society, the Philadelphia College of Physicians and other local organizations.

On motion by Dr White, seconded by Dr Stroud, and regularly carried, it was *Resolved*, that we discontinue inviting all the members of the local medical societies to register for attendance at the local clinics, due to overcrowding the members of the College for whom the program is arranged. It shall be provided, however, that the general sessions and, at the Philadelphia Session, the two lecture rooms in the auditorium be open for the free admission of all members of the County Medical Society and the members of the Philadelphia College of Physicians.

Dr Jonathan C Meakins, President of the College, reported upon the preparation for the general program of the Philadelphia Session. He reported that he proposes to have fewer papers, somewhat longer recesses in the middle of the afternoon meetings and to provide more freedom from scheduled meetings. He proposes to publish in the program the exact time for the appearance of each speaker, so that anyone who wants to hear a particular paper can tell definitely when the speaker will appear. Dr Meakins further said that he had delayed making up the program of general sessions, so that all the material he accepts will be strictly up to date and the result of recent investigation.

The Executive Secretary reported that the physical arrangements have been taken care of, the Benjamin Franklin Hotel selected for hotel headquarters and the Municipal Auditorium for general headquarters and the meeting place for general sessions. The commercial exhibits will also be housed there. The exhibit charts were prepared some weeks ago, and more than two-thirds of the space has been contracted for by firms who will exhibit. He asked the feeling of the Board of Regents concerning the initiation of scientific exhibits, pointing out that such exhibits are fairly expensive and require much time and effort. No scientific exhibit should be initiated unless it will be of the highest quality. It seems that the conduct of the scientific exhibits should more or less be given to the American Medical Association, which has already conducted many such exhibits on a very high scale.

On motion by Dr Piersol, seconded by Dr White, and regularly carried, it was *Resolved*, that the College shall not at the present time embark upon the plan of conducting scientific exhibits.

On motion by Dr Meakins, seconded by Dr Warren, and regularly carried, it was *Resolved*, that the College of Physicians of Philadelphia be extended a vote of thanks from the Board of Regents of the American College of Physicians for their hospitality on the occasion of the Weir Mitchell Dinner on December 15, which our Board attended as a body.

The Board of Regents authorized the Committee on Credentials to hold a meeting on or before the end of March 1935, for the purpose of reviewing all proposals for membership to be acted upon during the Philadelphia Session.

Adjournment

Attest E R LOVELAND,
Executive Secretary

COLLEGE NEWS NOTES

NOMINATIONS FOR ELECTIVE OFFICERS

The Committee on Nominations of The American College of Physicians, in accordance with the provisions of the By-Laws, presents the following nominations for the elective officers of the College for 1935-1936

President-Elect, Ernest B Bradley, M D , Lexington, Ky
First Vice-Pres , Arthur R Elliott, M D , Chicago, Ill
Second Vice-Pres , David P Barr, M D , St Louis, Mo
Third Vice-Pres , James S McLester, M D , Birmingham, Ala

Respectfully submitted,

Committee on Nominations,
CHARLES F MARTIN, *Chairman*
ROGER I LFE
WILLIAM J KERR
CHARLES H COCKE
GERALD B WFPB

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Dr Ralph Pemberton (Fellow), Philadelphia, Pa—one book, "The Medical and Orthopaedic Management of Chronic Arthritis",

Dr Henry P Wright (Fellow), Montreal, Que—one book, "Essentials of Infant Feeding and Paediatric Practice"

Acknowledgment is also made of the receipt of reprints from the following

Dr Ralph Oakley Clock (Fellow), New York—1 reprint,

Dr Howard L Hull (Fellow), Yakima, Wash—1 reprint,

Dr Paul H Ringer (Fellow), Asheville, N C—4 reprints,

Dr Albert H Rowe (Fellow), Oakland, Calif—8 reprints

Dr John C Ruddock (Fellow) Los Angeles, Calif—3 reprints,

Dr Vincent J Dardinski (Associate), Washington, D C—7 reprints,

Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint

Major J R Darnall (Fellow) vacated, January 15, 1935, the office of Secretary-Treasurer of the Medical Association of the Isthmian Canal Zone, Panama, and was installed as Vice-President for 1935 Major James S Simmons (Fellow), was installed as Secretary-Treasurer The scientific program included an address by Major Darnall on the subject of "Diabetic Coma," and a presentation by Major J G Knauer (Associate), of electrocardiographic studies of "Some Interesting Cases of Coronary Thrombosis"

Dr James L McCartney (Fellow), formerly Director of the Northwest Retreat, Portland, Ore, has been appointed Director of the Institute for Mental Hygiene of the Battle Creek Sanitarium, Battle Creek, Mich He will be in charge of the psychiatric work at the Sanitarium The Sanitarium for some time has planned to establish a Department of Psychiatry, and with the appointment of Dr McCartney, a modern psychiatric hospital of 75 beds is being opened to care for the constantly increasing demand for better facilities to treat nervous and mental cases

The Thirty-First Annual Congress on Medical Education, Hospitals and Licensure was held at Chicago, February 18 to 19, 1935 Dr James Alexander Miller

(Fellow), Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York, presented a paper on "Education of Physicians in Tuberculosis"

Dr L J Moorman (Fellow), Dean, University of Oklahoma School of Medicine Oklahoma City, presented a paper on "Some Historical Aspects of Tuberculosis"

Dr J A Myers (Fellow), Professor of Medicine, Preventive Medicine and Public Health, University of Minnesota, Minneapolis, presented a paper on "Function of the General Hospital in the Treatment of Tuberculosis"

On the subject "Should the Radiologist, the Pathologist, and Anesthetist be Licensed to Practice Medicine?", Dr B R Kirklin, Rochester, Minn, presented the case from the standpoint of the radiologist, Dr James S McLester (Fellow), Birmingham, Ala, from the standpoint of the internist, and Dr Walter L Bierring (Fellow), Des Moines, Ia, from the standpoint of the licensing board

Dr Harold Rypins (Fellow), Secretary, New York Board of Medical Examiners, Albany, presented a paper on "Are Interns Practicing Medicine?"

Dr Daniel J Glomset (Fellow), Des Moines, Ia, with Dr Charles Gordon Heyd of New York, presented a paper on "Extension Teaching in Medicine"

Other Fellows of the College, who appeared on the program to discuss various papers, were

Dr Irving S Cutter, Chicago
 Dr Willard C Rappleye, New York
 Dr Henry C Sweany, Chicago
 Dr James J Waring, Denver
 Dr Kennon Dunham, Cincinnati
 Dr Edward S McSweeney, New York
 Dr Albert Soiland, Los Angeles
 Dr J J Moore, Chicago

Dr R W Bradshaw (Associate), College Physician to Oberlin College, Oberlin, Ohio, was reelected President of the American Student Health Association at its last annual meeting in New York, December 27 to 28, 1934

Dr Hyman I Goldstein (Associate), Camden, N J, has been appointed a member of the Editorial Board of the Review of Gastroenterology (New York), and is Vice-Chairman of the Abstract Staff

OBITUARIES

JOHN ROWAN MORRISON

On the eighth of January, 1935, Dr John Rowan Morrison, F A C P, died after an illness of several months. He was born in the year 1877 in Oldham County near Louisville, Kentucky, not only of pioneer Kentucky stock but of pioneer physicians stock as well. His father, Dr A M Morrison, was an eminent Federal army surgeon in the war between the states, and two of his maternal uncles were physicians. He was a graduate of the old Louisville Medical College in 1898, and his postgraduate work was done in New York City at the Hospital for Ruptured and Crippled and later at Bellevue. After his internships Dr Morrison returned to Louisville and despite the fact that he had been crippled since childhood by poliomyelitis he engaged in hard general practice for more than 20 years, later limiting his work to the field of internal medicine. Always progressive, he was one

of those responsible for the medical certification of milk, and for dairy herd testing in Kentucky. He assisted in the organization of Public Health Nursing in Louisville and in many other useful enterprises. Dr Morrison was a valued teacher at the Louisville Medical School where he was a Clinical Professor of Medicine and his ward rounds have impressed upon many a medical student the value of original thinking and the avoidance of fads. An astute clinician, he arrived at a correct diagnosis quickly and accurately, and was much esteemed as a consultant.

Dr Morrison was greatly loved for his kind encouragement to young physicians, cordially welcoming them into practice and helping them in many ways if he considered them worthy. He highly prized his Fellowship in the College of Physicians and was always interested in securing good men for the College in this community. Not only a skilled physician but a man of wide culture, a philosopher and a wit, his fellowship will be badly missed.

HARRY S. FRAZIER, M.D., F.A.C.P.,

Louisville, Ky

E. RODNEY FISKE

Dr E. Rodney Fiske, Fellow of the American College of Physicians since 1925, died December 19, 1934, of Hodgkin's disease. He was born in Brooklyn in 1873, received his preliminary education at the Brooklyn Polytechnic Institute, his B.A. degree from Columbia University, and his medical degree from the New York Homeopathic Medical College in 1895.

Dr Fiske had served many hospitals and institutions during his career. At the time of his death he was associate professor of medicine at the New York Homeopathic Medical College and Hospital, associate attending physician to the Flower Hospital, consultant to the Yonkers (N. Y.) General Hospital, Brooklyn Nursery and Infants Hospital, and the Huntington (N. Y.) Hospital, and, chief of the department of medicine, Peck Memorial Hospital of Brooklyn.

He was a member of the Kings County Homeopathic Medical Society, New York State Homeopathic Medical Society, Academy of Medicine of New York, and the American Institute of Homeopathy. He was a member also of the Phi Beta Kappa honorary fraternity and a founder of the Alpha Sigma professional fraternity.

KENNETH G. MOWAT

Dr Kenneth G. Mowat, Associate, of Buffalo, New York, died January 13, 1935, of a heart attack.

Dr Mowat was born in 1885 and graduated from the University of Buffalo School of Medicine in 1924. He was an instructor in medicine in his Alma Mater. He was a member of the Erie County Medical Society, New York State Medical Association, Buffalo Academy of Medicine and the American Medical Association. He was elected an Associate of the American College of Physicians during 1928.

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THE INFLUENCE OF DIETETIC AND OTHER FACTORS ON THE SWELLING OF TISSUES IN ARTHRITIS

PRELIMINARY REPORT

By C W SCULL, Ph D, and RALPH PEMBERTON, M D, F A C P,
Philadelphia, Pennsylvania

IN 1927 Peirce and Pemberton¹⁵ reported data indicating that, following a stab of the finger, fewer red cells per cubic millimeter are found in the first several drops of blood of patients with severe arthritis, as compared with subsequent drops. While this difference is sometimes discovered in normal persons and in patients with mild arthritis, it is less frequent. Several possible explanations of this phenomenon have been advanced, namely, that the capillaries of normal persons are open in larger numbers, that the first issuing blood in arthritic patients is diluted in the vessels, and, that the normal or decreased number of cells in the vessels is scattered and dispersed through increased or normal amounts of serous fluids from the tissues as they issue forth.

Investigating the last mentioned possibility, Peirce, Wright and Pemberton attempted to determine the rapidity with which normal salt solution injected intradermally in the arthritic patient would be absorbed as compared with normal persons (not yet reported). McClure and Aldrich have shown that in the presence of edema there may be such an apparent avidity of the tissues for fluid that normal salt solution injected intradermally is dissipated more rapidly. The results of these experiments, however, were not sufficiently clear-cut to permit of precise evaluation, and further observations are pending. The general problem involved, however, has been brought to the fore again by other considerations which will be briefly discussed.

In a recent publication Pemberton, Peirce and Bach¹⁴ have adduced evidence indicative of the prompt subsidence of the inflammatory or swollen tissues of the arthritic following dietetic control in suitably selected cases. They stated that a response of this nature is probably to be observed more

* Reported in brief before the Chicago Club for the Study of Arthritis, January 12, 1934, and before the American Gastro-Enterological Association, April 30, 1934.

promptly under these circumstances than following any other line of therapy, with the possible exception of convalescence following the removal of focal infection in very early sthenic cases. Changes may be observed as early as 24 hours following the institution of dietetic therapy and may become very graphic at the end of three or four days. This has also been previously stressed elsewhere by Pemberton.⁸

In conjunction with his associates, one of the writers has published a considerable series of studies indicating that various physiological disturbances accompany or characterize arthritis, and the American Committee for the Control of Rheumatism has expressed itself as believing that arthritis in general is a systemic disease with joint manifestations. Furthermore, in many cases of arthritis the phenomena within and around the joints are almost negligible, being greatly overshadowed by such clinical states, with the involvement of other tissues, as come under the head of myositis, neuritis, disease of the uveal tract, mental hebetude, fatigue, neurasthenia and even psychoses.

Another matter requires mention at this point. Pemberton⁹ has recently pointed out that the classical syndrome of arthritis may be regarded as characterized by imbalance of at least three of the major systems of the body, viz. the circulatory, nervous and gastrointestinal. Several lines of observation, at the hands of a number of students of arthritis, justify this conclusion. (Wright, Pemberton¹⁰ on peripheral circulatory changes, Fletcher and Graham³ and Pemberton and collaborators on gastrointestinal disturbances^{8, 13, 14}, Rowntree, Adson¹⁶ on nervous system dysfunctions.)

Clinical appreciation of some phases of this conception has long found expression in the views of Goldthwaite, Osgood, Swain and their collaborators as to a probable "pooling" of blood in the arthritic, at least of the atrophic type. On the basis of this and other considerations these workers have advocated various postural attitudes and exercises which are accepted as having important clinical consequences. Sparks and Haden have also recently observed an increased blood volume in atrophic arthritis.¹⁷

We have been impressed with the importance of systemic rest in the therapy of arthritis, and we now regard rest in recumbency not in the vague sense of avoidance of overactivity or fatigue, but in a specific sense as contributory to changes in the gravitational influences. These are most easily appreciated in connection with the dynamics of the circulatory system, including particularly the capillary beds, but also have an equally important bearing upon the gastrointestinal and, at least clinically, upon the nervous system as well. It may be remarked, parenthetically, that in the course of observations upon soldiers in service, Pemberton¹⁰ showed that the arthritic, as compared with the normal under similar conditions, presents a very slight lag in the elimination of water, nitrogen and particularly salt when subjected to the so-called nephritic test meal.

In planning the experiments here reported, it was decided therefore to include also observations upon patients admitted to the hospital and at once

given complete rest, since in properly selected cases the subsidence of swelling referred to above can be early detected under these circumstances

Viewing a series of these patients undergoing successful therapy especially along nutritional lines, and having the above several considerations in mind, several clinical phenomena are to be observed, the possible significance of which has apparently largely or wholly escaped notice. These phenomena consist first of the subsidence of supposedly inflammatory tissue along the proximal and middle phalanges of many or all fingers and of the subsidence of swelling on the dorsum of the hand, beginning on the ulnar aspect. Subsidence of the swollen tissues surrounding the shafts of the phalanges may give rise to a relative increase in prominence of articular and periarticular enlargements at the phalangeal articulations, especially in the hypertrophic type. Subsidence of the dorsal tissues of the hands, however, leads to a collapsed or "all gone" appearance which renders visible, slowly but progressively, the tendons of the metacarpus.



Fig 1



Fig 2

FIG 1 Photograph of hand of arthritic patient before experimental period of low caloric feeding

FIG 2 Hand of the same arthritic patient after experimental period of low caloric feeding

While the collapse of tissues is evident to a critical observer it is difficult to obtain striking photographic illustration of the subsidence of swelling. However, as illustrative of the type of change taking place under the

influence of dietetic measures which will be discussed later, photographs taken at the beginning and at the conclusion of an experimental period are shown in figures 1 and 2

There takes place at the same time a progressive recession of swelling in the dorsal tissues of the hand, from the metacarpo-phalangeal articulation toward the carpus itself. At a certain stage of subsidence, the metacarpal tendons may be uncovered across the dorsum of the hand from the knuckles to a point midway between the knuckles and the wrist. The residual zone of swelling, above the hand, in turn slowly recedes upward until inspection and palpation of the hand as a whole reveal nothing but the underlying bony and tendinous structures covered by the integument itself. Conversely, exacerbations of the arthritis are accompanied by a return of swelling in the non-articular soft tissues. The process under discussion is best seen at an intermediary stage when contrasts are evident between the subsided and the unsubsided tissues. The possibility of such a subsidence on the dorsum of the hand may not suggest itself at the outset, as the hand does not necessarily or usually appear swollen. Similarly, after subsidence, nothing is obvious to suggest the previous state. Thickness and swelling, when present, of the metacarpo-phalangeal articulations likewise undergo retrogression. There is therefore a fairly close correlation between the activity of the arthritic process and the phenomenon of tissue swelling. This question is discussed in detail because it is believed that it has not been the subject of adequate scrutiny.

The nature of this swelling awaits explanation. Inasmuch as the tumefaction also concerns regions, such as the dorsum of the hand, where there are no joints, it must be regarded as something partly extraneous to the joints themselves. Furthermore, these regions are not the seat of pain such as usually characterizes the joint structures themselves in the course of arthritis. One plausible explanation is therefore that the condition under observation reflects a systemic disturbance which does not partake of an inflammatory nature in the sense usually understood by that term. The mobility of the swelling suggests further the possibility that it may represent in part at least an abnormal accumulation of fluids, and the observations recorded below were undertaken to determine whether such a view might be tenable. Inasmuch as satisfactory procedures for the direct quantitative estimation of fluids in the structures involved were not immediately available, recourse to an indirect method seemed necessary. As a preliminary step observations on the approximate water balance have been made whereby gross retention or release of fluid by the body as a whole might be measured during the course of therapy primarily dietetic in nature. The recent review by Adolph¹ on water metabolism and distribution in tissues has directed attention to the possibility that some of the dietetic and other measures used in the treatment of arthritic patients may have exerted among other effects a significant influence on the distribution of water in tissues.

In view of the above considerations, studies were conducted upon the

daily water exchange in 30 arthritic patients whereby an approximate estimate of the gain or loss of fluid by the body might be obtained. The subjects were selected from among the atrophic and hypertrophic patients, admitted to the arthritis service, who seemed most likely to exhibit the above mentioned reduction of soft tissue swelling. The state of the tissues with respect to extent of swelling, pain and limitation of motion, was recorded on the basis of clinical observation, usually corroborated or checked by several persons. The method for calculating the gain or loss of water is semi-quantitative.

As indicated in table 1, the gain or loss of water is determined by subtracting the total water output from the total water intake. The water intake includes the water drunk as such and the water derived from the food. The latter factor represents the total amount of water served to the patient and the water which is produced in the body by the combustion of the carbohydrate, fat and protein in any dietary mixture. The former fraction, the water present as such in the food, is designated as preformed water, and the latter, the water produced by combustion within the body, as water of oxidation. The total water output includes the quantities eliminated through the kidney in the urine, through the bowel in the feces, through the skin and lungs in the form of sweat and water vapor.

TABLE I
Outline of Procedure for Calculation of Approximate Water Balance
Daily water exchange

| <i>Intake</i> | | <i>Output</i> | |
|---|-------|------------------------------|-------|
| Water as such | | Urine | |
| Volume measured | _____ | Volume measured | _____ |
| Water from food | | Feces | |
| Servings weighed | | Weight (gm) \times % water | _____ |
| Composition calculated | | | |
| Preformed water | _____ | Skin and lung loss | |
| Water of oxidation | _____ | Estimate heat production | |
| Protein (gm) \times 0.413 | _____ | H.P. (Cal) \times 0.6 | _____ |
| Fat (gm) \times 1.07 | _____ | | |
| Carbohydrates (gm) \times 0.555 | _____ | | |
| TOTAL | _____ | | _____ |
| "Approximate Water Balance" = Total Intake - Total Output | | | |

The contributory factors constituting the total water loss are more or less evident, except perhaps, the indirectly calculated estimate of the skin and lung loss. Direct determinations of the insensible losses were not made because of the fact that scales suitable for weighing patients with a sensitivity of a few grams were not available. In view of this, use was made of the empirical generalization of Benedict and Root² that the insensible loss

is a function of the heat production. The factor of 0.6 c.c., water lost per calorie of heat production, is taken from data presented by Adolph.¹

The fact that the activity of the patients under observation in the present series was relatively constant from day to day is believed to justify the use of this arbitrarily determined constant. It is recognized that the approximation of water calculated according to the above procedure falls short of the more complete and more nearly accurate estimate outlined by Wiley and Newburgh¹⁸ but as a practical expedient it seems adequate to reveal the contrasts upon which the present studies are based. In this general connection it is important to note that, with the deposition of one gram of protein or carbohydrate in the tissues, approximately three grams of water are stored. The storage of one gram of fat is associated with the deposition of one-tenth gram of water. During starvation, the tissues are of necessity broken down to supply energy for metabolism and incidentally the water bound by the substances catabolized is released. Under such circumstances there would be a net loss of water from the body. During periods of low caloric supply a negative water balance develops on the basis of the above premises. In view of these facts the food intake and the water balance are correlated with the clinical findings in the following cases.

TABLE II

Daily Water Exchange in an Atrophic Arthritic Under Conditions of Recumbent Rest, Slightly Modified Diet and Ward Care

| Day of Observation | Diet | | | Total Calories | Total Water Intake | Total Water Output | Balance |
|--------------------|------|-----|-----|----------------|--------------------|--------------------|---------|
| | P | F | C | | | | |
| 1 | 59 | 82 | 134 | 1506 | 1559 | 2150 | -590 |
| 2 | 70 | 97 | 129 | 1661 | 2300 | 2810 | -510 |
| 3 | 54 | 55 | 174 | 1406 | 1790 | 2460 | -690 |
| 4 | 77 | 106 | 149 | 1860 | 2380 | 2398 | -18 |
| 5 | 69 | 77 | 136 | 1514 | 3055 | 2745 | +310 |
| 6 | 88 | 106 | 169 | 1973 | 2170 | 2520 | -350 |
| 7 | 60 | 79 | 243 | 2095 | 2205 | 2300 | -95 |
| 8 | 88 | 98 | 314 | 2470 | 2307 | 2540 | -233 |
| 9 | 84 | 119 | 216 | 2271 | 2204 | 2170 | +34 |
| 10 | 66 | 94 | 158 | 1744 | 2462 | 2665 | -203 |
| 11 | 77 | 78 | 221 | 1943 | 2484 | 2260 | +224 |
| 12 | 64 | 117 | 126 | 1811 | 2109 | 2780 | -671 |
| 13 | 60 | 111 | 112 | 1690 | 1913 | 2055 | -142 |

Estimated caloric requirement 1700 cal/24 hours. A progressive decrease in swelling, pain and limitation of motion occurred, the most rapid change taking place during the first few days.

In order to illustrate the general trend of the daily fluid exchange with respect to the clinical phenomenon of tissue swelling, data of a representative case of atrophic arthritis indicating an apparent systemic loss of fluid coincident with a decrease in tissue swelling, pain and limitation of motion, are presented in table 2.

Of the several possible factors contributing to the above result the influence of the inadequate caloric intake voluntarily selected from the house diet by the subject must be considered. The following three cases illustrate the uncomplicated results of the reduced caloric intake. Each of the three patients in this group made significant advances during a preliminary period in the hospital, but at the time of the experimental period had reached a state of equilibrium with residual swelling.

In table 3 (case Bkf) are shown the findings in such a stabilized case, indicating that a sharp curtailment of calories results in a net loss of water from the body. This patient at the time of this observation had been a bed-ridden invalid for 20 months and it is possible, therefore, to discount all essential influences referable to posture, the prone position, etc. The diet consisted of orange juice, milk for breakfast and lunch, and a light, mixed but balanced, dinner. Coincident with the apparent water loss there was a reduction of tissue swelling. Like changes were observed in similar cases on correspondingly reduced food intakes.

TABLE III

Daily Water Exchange in Arthritic Cases Subjected to Low Caloric Intake

| Name | Time in Bed Before Experi- mental Period Mo | Diet | | | Calories | Water Balance | Swelling Pain |
|------|--|------|-----|-----|----------|------------------|------------------|
| | | P | F | C | | | |
| Bkf | 20 | 47 | 81 | 121 | 1400 | +200 | Decreased |
| | | 23 | 37 | 93 | 800 | -175 | |
| | | 30 | 38 | 97 | 800 | -175 | |
| | | 44 | 103 | 98 | 1500 | +200 | |
| Fkln | 1 | 51 | 125 | 117 | 1800 | -174 | Decreased |
| | | 51 | 125 | 117 | 1800 | - 58 | |
| | | 17 | 16 | 71 | 500 | -1050 | |
| | | 17 | 16 | 71 | 500 | -349 | |
| | | 44 | 131 | 108 | 1800 | +335 | |
| | | 44 | 131 | 108 | 1800 | +328 | |
| Ce | 1 | 12 | 2 | 102 | 470 | - 35 | Reduced |
| | | 17 | 2 | 122 | 570 | -591 | |
| | | 21 | 11 | 148 | 675 | -251 | |
| | | 74 | 126 | 121 | 1910 | +250 | |
| | | 74 | 126 | 121 | 1910 | +635 | |

Estimated calories required Bkf 1400, Fkln 1600, Ce 1900

Table 3 (case Fkln) shows the coincident reduction of swelling and net water loss under the influence of a low caloric liquid diet consisting solely of orange juice and milk. It may be noted in passing, that a negative water balance occurs even in the presence of an unrestricted supply of water, under the conditions of a so-called fluid diet which provides a submaintenance total of calories. This is obviously referable to the fact that the tissues are called upon to supply the deficit of energy and incidentally yield the water with which the protein, fat and carbohydrate are combined.

The data of these two cases serve to emphasize the fact that dietetic measures may be utilized to induce further improvement in patients who have already been given the benefit of the sum of factors involved in a regimen including recumbent rest. In each case sufficient time had elapsed before the dietetic measures were brought to bear for a more or less stable equilibrium to be attained, and it appears reasonable therefore to attribute the change noted to the reduced caloric intake uncomplicated by the physiological effects incident to postural changes. Further considerations bearing on this point will be mentioned later.

Table 3 (case Ce) shows the effect in one patient of the vitamin-free diet, consisting of crackers, gruel, and coffee, used by Pemberton, Peirce and Bach¹⁴ in a series of cases recently reported. This diet is not only low in vitamins but is likewise calorically inadequate. A negative phase of water balance is coincident with the period of underfeeding. While this particular patient, in whom the most evident swelling consisted of an effusion in the knee, did not exhibit a distinct decrease in tissue swelling in the sense here understood, the deduction is unavoidable that similar systemic losses of water occurred in all of the patients included in the preceding series¹⁴. A positive correlation of the observed rapid subsidence of tissue swelling with a negative water balance during the experimental diet periods presumably existed, therefore, in the series cited¹⁴.

The data presented suggest that the phenomenon of reduced tissue swelling is, under the conditions described, associated with nutritional factors involving a net loss of water from the body. The question may still be raised whether the subsidence of swelling during dietetic measures is due to (1) a physiological variation of normal tissue substance and fluids, (2) a loss of pathological cellular tissue substance, or (3) a loss of a pathological surfeit of fluid. The first factor does not appear adequate in explanation because of the fact that the swelling tends to remain subsided in the post-experimental periods following the physiological "pickup" of the bulk of the water lost.

The data available at present are insufficient to provide an adequate basis for choice between the two last mentioned possibilities, although the evidence is suggestive of the existence of a pathological surfeit of extra-cellular fluid. In further support of the view that something more than a normal physiological loss of water is involved, one experiment is cited in which an approximate estimate of the fluids released from the breakdown of normal tissues has been made.

Table 4 (Mrs Sm) shows data on the fluid balance in a series of observations wherein technical errors seem to be at a minimum. While it is realized that the metabolic mixture derived from tissues must contain certain quantities of carbohydrate, data on the respiratory quotient are not at hand to indicate this ratio, and it is necessary to utilize the approximation outlined below.

TABLE IV

Daily Water Exchange in a Patient Who Exhibited a Subsidence of Tissues on a Submaintenance Diet Although Stabilized with Respect to Effects of Posture

| Day of Obs | Diet | | | Cal-ories | Esti-mated Caloric Output | Nitrogen | | Tissue Loss | | Water from Break-down of Tissue | Water Bal ¹ | Water Bal |
|------------|------|----|-----|-----------|---------------------------|----------|--------|-------------|----|---------------------------------|------------------------|-----------|
| | P | F | C | | | Intake | Output | P | F | | | |
| 1 | 45 | 31 | 125 | 962 | 1350 | 7.2 | 10.3 | 19 | 35 | 97 | -484 | -387 |
| 2 | 44 | 49 | 89 | 980 | 1350 | 7.0 | 10.8 | 24 | 31 | 117 | +331 | +448 |
| 3 | 49 | 40 | 104 | 962 | 1350 | 7.8 | 11.2 | 21 | 34 | 112 | -923 | -811 |
| 4 | 49 | 37 | 85 | 869 | 1350 | 7.8 | 11.4 | 23 | 43 | 116 | -542 | -426 |
| 5 | 55 | 48 | 96 | 1036 | 1350 | 8.8 | 10.3 | 9 | 30 | 69 | -431 | -362 |
| 6 | 54 | 36 | 116 | 1008 | 1350 | 8.6 | 10.1 | 9 | 34 | 71 | -190 | -119 |

¹ Water balance calculated according to procedure outlined before

² Water balance calculated according to scheme in text

An approximation of the amount of water derived from the breakdown of cellular tissues has been made on the basis of the general premises indicated earlier as being operative during periods of submaintenance. The calorie deficit between the diet and the estimated energy output has been assumed to be made up by tissue breakdown, with corresponding release of water. It is assumed that the negative nitrogen balance measures the protein loss. The amount of calories supplied by the tissue protein subtracted from the calorie deficit is taken as representing the fat burned. On the basis of these figures the amount of water released by the breakdown of the protein and fat is calculated by considering that three grams of water are derived from one gram of protein and one-tenth gram of water from each gram of fat. By adding to the sum of those quantities the amounts of water derived by oxidation, according to the method detailed in chart 1, the total amount of water from the tissues is estimated. From this estimate it appears that extracellular tissue water contributed significantly to the net loss of water from the body under the conditions of a slightly submaintenance diet in a patient long previously stabilized with respect to the effect of posture.

If the phenomenon of reduction of swelling of tissues as here understood be related to systemic water loss, it might be expected that diets so devised as to be additionally dehydrating would induce even more marked clinical changes. Diets which approximate, in the percentage of the three foodstuffs, the endogenous metabolic mixture utilized by the body consequent upon conditions of submaintenance might therefore be useful for this purpose, that is to say, diets relatively high in protein or high in fat as compared with the ordinary high carbohydrate supply. It might be noted here that the balanced diet recommended by one of the present authors usually entails a reduction of the carbohydrate and a relative increase in the fat and protein as compared with the average dietary. From this point

of view the experimental diets here discussed may be considered as extreme variants of the type of "arthritic" diet most commonly used

In order to illustrate the relationship of the protein and fat, several patients were accordingly placed on diets isocaloric with the preliminary diets but relatively increased in protein or fat

Table 5 (case Shck) shows typical findings in a subject, previously equilibrated with respect to posture, upon a diet relatively increased in protein. The diet was prepared with a minimum amount of salt and the fluid intake was restricted. An apparent loss of water occurred with the observed reduction in tissue swelling. It should be noted in passing that this patient exhibited a subsidence of tissue swelling of the type here discussed despite the fact that she presented definite and advanced hypertrophic arthritis as shown by roentgenograms of the hands and knees. There was no cardiac decompensation.

TABLE V
Approximate Water Exchange as Influenced by Qualitative Character of Diet

| Patient | Day | Diet | | | Calories (Intake) | Calories (Output) (Calculated) | Water Balance | Swelling Pain |
|---------|-----|------|-----|------------------|----------------------|--------------------------------------|------------------|-------------------------|
| | | P | F | C | | | | |
| Shck | 1 | 55 | 112 | 192 | 2000 | 1700 | +398 | Decreased |
| | 2 | 46 | 74 | 84 | 1180 | 1700 | (-50) | |
| | 3 | 100 | 100 | 100 ¹ | 1700 | 1700 | -421 | |
| | 4 | 100 | 100 | 100 ¹ | 1700 | 1700 | -274 | |
| | 5 | 50 | 100 | 150 | 1700 | 1700 | +52 | |
| | 6 | 55 | 95 | 125 | 1625 | 1700 | -165 | |
| Danr | 6 | 60 | 102 | 111 | 1774 | 1500 | +244 | Progressive decrease |
| | 7 | 80 | 102 | 114 | 1786 | 1500 | -298 | |
| | 8 | 59 | 103 | 115 | 1795 | 1500 | +162 | |
| | 9 | 53 | 163 | 15 | 1735 | 1500 | -810 | |
| | 10 | 53 | 163 | 15 | 1735 | 1500 | +268 | |
| | 11 | 53 | 163 | 15 | 1735 | 1500 | -214 | |
| | 12 | 53 | 163 | 15 | 1735 | 1500 | -250 | |
| | 13 | 63 | 119 | 115 | 1782 | 1500 | +778 | |
| | 14 | 60 | 122 | 116 | 1799 | 1500 | +478 | |
| | 15 | 58 | 112 | 107 | 1730 | 1500 | +37 | |

¹ Low in salt, fluid intake restricted

It is to be further observed that two of the cases in the series here presented showed unmistakable and uncomplicated evidences of hypertrophic arthritis. In some other cases, previously seen to respond in the same way to the nutritional principles involved, the type was equally definitely hypertrophic. Two illustrative roentgen-rays are appended, one of atrophic and the other of hypertrophic arthritis (figures 3 and 4). The implication is therefore clear that both types of the disease must be regarded as presenting, in some cases at least, the phenomenon of excess tissue fluids, and also, that both types respond about equally to the same therapeutic influences discussed above.

Table 5 (case Danr) shows the results in a case subjected to a ketogenic diet. This patient experienced a progressive decrease in swelling and pain during the period of observation. However, there was seemingly a slight acceleration in the rate of improvement during the period of increased water



Fig 3



Fig 4

FIG 3 Roentgenogram of hands of an atrophic arthritic patient (Bkf)

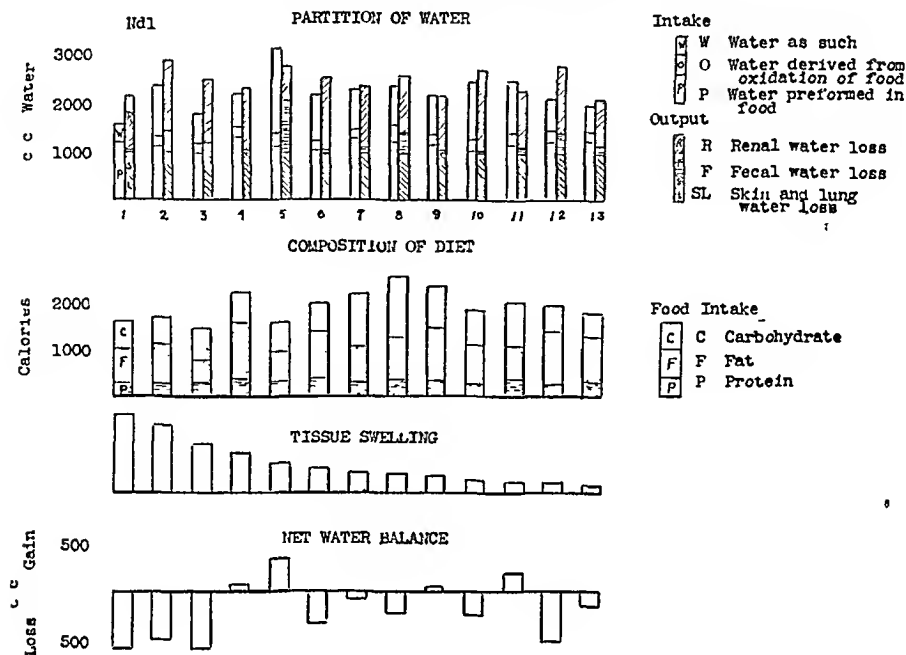
FIG 4 Roentgenogram of knee of a hypertrophic arthritic patient (Shck)

loss while on the ketogenic diet. The slight acceleration in rate of recovery in this and one other case (C Sm) during a ketosis imposed by dietary means is not now to be considered a recommendation for the therapeutic application of such a diet. Further studies in this connection are pending.

Such observations as the above series affords again indicate the necessity for taking into account the influence of dietetic factors which may be incidental to other therapeutic measures.⁸ Further evidence is thus adduced that the early onset of objective improvement from surgical procedures, such as tonsillectomy, for example, is sometimes related to the nutritional state incidently imposed rather than to the operation per se. The influence of nutritional factors is probably operative in all cases and may be conspicuous if the early clinical betterment, often experienced by patients as observed objectively, is not maintained. During or following recovery from an operation which has not removed the cause of the arthritis, the patient usually returns to a fuller dietary, and swelling and pain may then gradually return. Instances of this are legion in the experience of every close observer of arthritis.

CHART I

Daily Water Exchange in a Case of Arthritis under Conditions of Recumbent Rest, Slightly Modified Diet and Ward Care



The favorable influence exerted on the patients by recumbent rest has already been mentioned as contributory to the clinical improvement noted in patients subjected to hospital care. It has been further emphasized that the favorable effect of bed rest represents the result of many physiological and mechanical factors. The extent and nature of their interrelationships as they bear upon the problem of arthritis require more extended consideration.

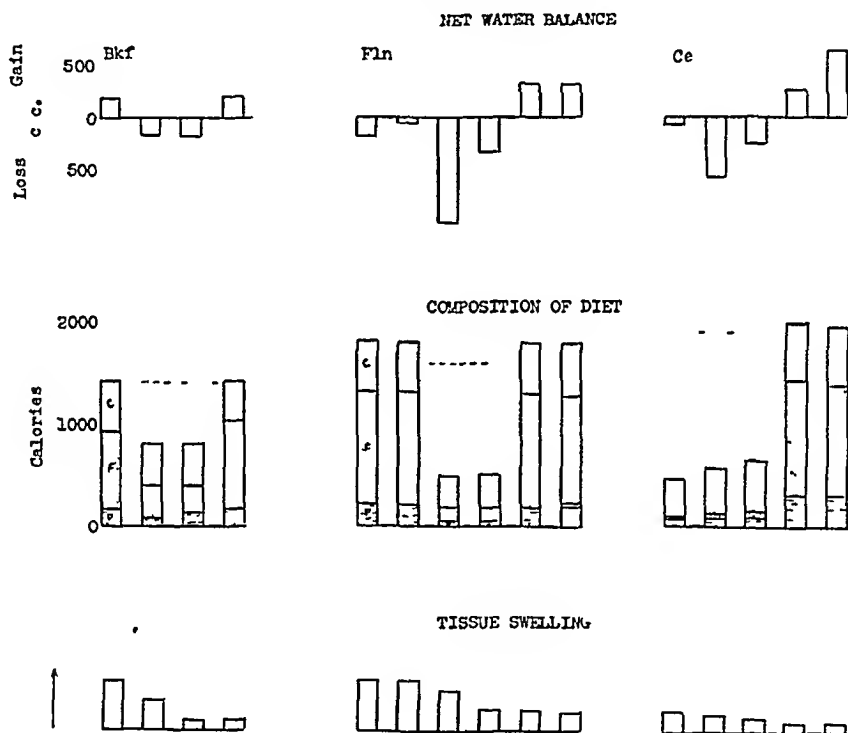
The various major systems of the body, namely, the circulatory, nervous, gastrointestinal and respiratory, are admittedly related to and interdependent upon each other. The reader need hardly be again reminded that the capillary beds in many of the tissues of the arthritic patient are more or less reduced. The normal condition of the circulation in the capillary beds of the gastrointestinal tract is probably a most important factor, but the state of the capillary beds elsewhere in the body is almost equally important in that this determines in part the distribution of the blood in the gastrointestinal tract and in various tissues where its respiratory and other functions are exercised.

Among arthritic subjects, in whom anatomical displacements and dysfunctions of the gastrointestinal tract are the rule as much as the exception, the relationships above indicated become even more significant. Inasmuch as the removal of gravitational influences achieved by the assumption of the supine rather than the erect posture profoundly alters conditions within the

circulatory system including conspicuously the capillary beds, it follows that these influences must presumably be reflected in the function of the various parts of the gastrointestinal tract as a whole. To this consideration may be added the fact, as pointed out elsewhere, that such departures from normal within the gastrointestinal tract as gastropnoxis, enteropnoxis and the like, with an attendant train of symptoms illustrated by hyperchlorhydria, are equally benefited by a position of recumbency in which previously operative gravitational influences are modified or removed.

CHART II

Daily Water Exchange in Arthritic Cases (Stabilized with Respect to Posture) Subjected to Low Caloric Diets



This brief recital of the influences which assumption of recumbency and betterment of the finer circulation exert upon patients, and even upon normal subjects, will suffice to indicate, as the experiments cited show, that the prescription of recumbency and a modified diet in arthritis constitutes reciprocals which cannot wholly be divorced one from the other.

Thus, under conditions characterized by gravitational handicaps it is sometimes necessary among these patients to reduce the load imposed by digestive and nutritional burdens to a minimum. Under conditions of restored gravitational equilibrium a greater nutritional and digestive burden may then often be assumed. After a certain departure from the normal is again reached, however, the nutritional and digestive burden must again be

reduced even though the favorable influence of gravitational and postural factors is at a maximum. This possibility is illustrated by three cases in the series.

It might be expected that a condition, which for the moment may be designated as excess fluid in the tissues, would be open to influence from several directions and this is indeed the case. It is therefore hardly necessary to point out the therapeutic corollary to these considerations, that the arthritic subject must be given the benefit of the several measures and influences which ameliorate the various manifestations of disturbed physiology.

One phase of the foregoing considerations relating to the effect of posture on the circulatory system may be considered in detail, the direction of the physiological transfer of fluid between the blood vessels and the tissue spaces following the assumption of various postures.

Krogh² and others¹ have shown that the assumption of upright posture is associated with an increased flow of fluid from the capillaries to the tissues, whereas the direction of fluid transfer may take place in the opposite direction in changing to the recumbent position. In conformity with the above, the present authors have observed changes in the specific gravity of the venous blood of arthritic patients when standing and when lying down. Average data are shown in table 6. This table indicates that there is an evident transfer of fluid to the tissues from the blood on standing and an exchange in the reverse direction on lying down. It is suggested that this mechanism contributes to the reduction of swelling when patients are placed on a régime which includes bed rest. Studies in the writers' laboratory indicate that a sufficiently refined technic for detecting possible differences between arthritic patients and normal controls in this respect is not yet available.

TABLE VI

Relation of Posture to the Direction of Fluid Transfer, as Shown by Specific Gravity of Venous Blood, Average of Five Cases

| Time (min.) | Position | Sp. Gr. Venous Blood Plasma |
|----------------|-----------|--------------------------------|
| 0 | Recumbent | 1.026 |
| 20 | Standing | 1.028 |
| 40 | Recumbent | 1.026 |
| 60 | Standing | 1.028 |
| 80 | Recumbent | 1.026 |

The suggestion is advanced on the basis of the preliminary data here presented, that the phenomenon of tissue swelling in arthritis may be regarded as one expression of the factors operative to induce other kinds of tissue swelling.

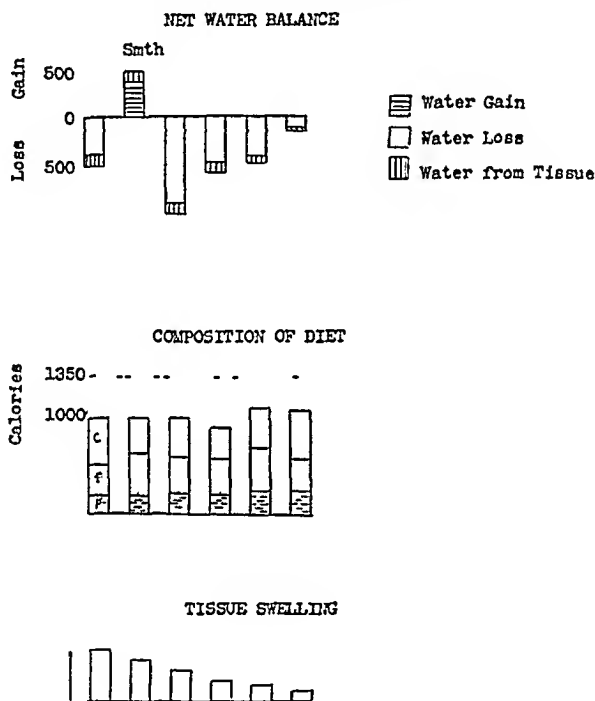
In accordance with the opinion that an abnormal fluid accumulation in the tissues contributes to the dynamic pathologic changes of arthritis, several apparently diverse factors known to exert an influence on the symptoms may be conceived as having a common basis.

The accumulation of tissue fluid may contribute to the decreased vari-

ability of the heat regulating function of the skin noted by Pemberton and Wright. The cold clammy hands of arthritics may be related to the same factor. Analogously, meteorologic changes which adversely influence symptoms may act through the lessened ability of the tissues of these patients to redistribute fluids readily. Similar considerations may apply to the decreased utilization of oxygen by the peripheral tissues¹¹ as well as to the delayed sugar removal^{10, 20}

CHART III

Daily Water Exchange in an Arthritic Case (Stabilized with Respect to Posture) Subjected to a Low Caloric Diet



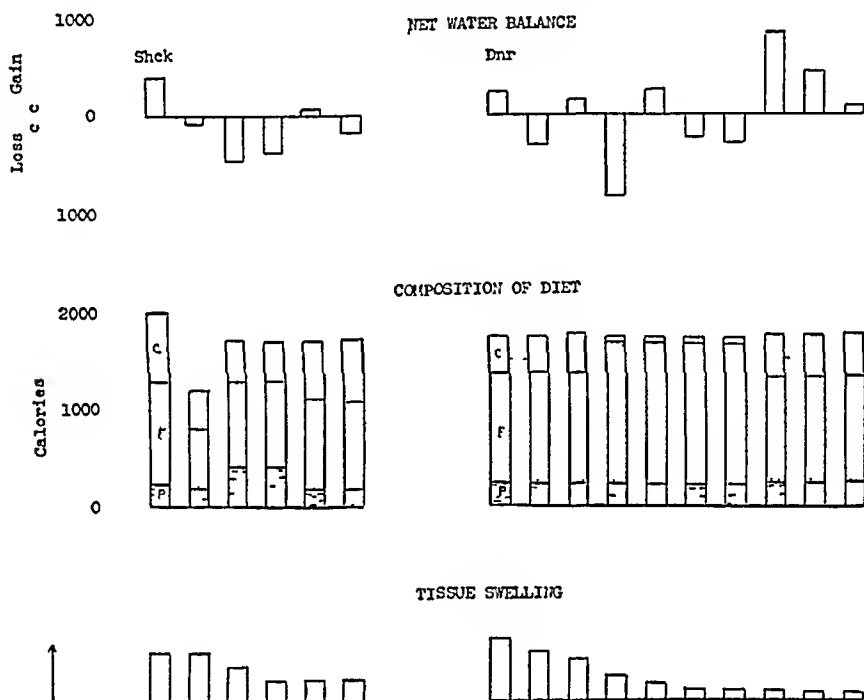
The slightly lowered basal metabolism encountered in about 33 per cent of arthritics^{4, 18} may depend in part upon an accumulation of inactive tissue fluid. The observation by Sparks and Haden¹⁷ of an increased plasma volume in atrophic arthritis further suggests that the relatively more fixed tissue-fluids are likewise increased. Many of the physical measures used therapeutically in the treatment of arthritis may achieve part of their benefit by the removal of fluid from tissues. Thus, local massage has been shown to increase urinary output²¹ perhaps by virtue of the increased lymph flow and circulation of blood which is induced. Heat acts to increase extrarenal losses and probably also acts to influence the local distribution of fluids.

Rest in recumbency is generally regarded as an effective means of bringing about a removal of fluid from the tissues in frank edema. While arthritic patients do not present derangements of the circulatory system to

an extent which leads to frank edema they do occasionally present very persistent local edema. Pemberton and Pence (unpublished) have observed in the skin capillaries a stasis or sluggish flow which might be considered as contributory to accumulation of fluid in the skin.

CHART IV

Approximate Water Exchange is Influenced by Qualitative Character of Diet



The recognized relationship of the plasma protein to the fluid accumulation in nephrosis suggested the desirability of determining the relation of plasma proteins to the type of swelling observed in arthritis. Experiments in the writers' laboratory, however, have failed to reveal any gross deviation from normal values for total protein among arthritic patients. The albumin-globulin ratios likewise appear to be within normal limits. There is, on the other hand, an increase in fibrinogen which is in general parallel to the increase in sedimentation rate. While the data do not permit a precise evaluation, it is possible that the increase of the protein fraction in plasma which alters the normal hydration of the red cells to the extent of increasing rouleau formation and the sedimentation rate, may also influence the distribution of fluids in tissues.

We believe that the swelling of tissues in arthritis is, in part at least, due to an excessive accumulation of fluids, and further, that dietetic and other measures which induce a reduction in swelling are associated with a net loss of fluid from the body.

Recognition of the probable participation of an abnormal distribution of fluid in the tissues, as part of the syndrome of arthritis, carries with it no implication that this explains the whole syndrome, nor should the implication follow that dehydration by any and all means constitutes a "cure" for arthritis. It is necessary only to point out that saline catharsis, intensive sweating and marked diuresis have been long and widely utilized, have been found to be only limited in value or even dangerous, and by general consent, do not as such constitute the "way out" for these patients. On the contrary emphasis should be placed upon measures or influences which operate in a more sustained way, without abrupt dislocation of function and without the imposition of further burdens.

Although clinical use of dietetic measures has had large substantiation in many hands and although laboratory studies of several kinds have adduced suggestive support, further precise data have been desirable. It is perhaps warranted, therefore, to point out that the considerations here advanced carry further justification for the use of these measures in the problem of arthritis. This is not to say, however, that the mechanism concerned in the influence of diet, above discussed, constitutes the only means by which dietary regulation may exert a beneficial influence in the treatment of arthritis. The experimental diets discussed are not to be confused with the optimal type of diet often necessary in treatment over long periods of time. Furthermore, the reader is hereby cautioned that the use of dietetic measures which we have described is not to be interpreted as a "blanket" form of therapy although probably having in principle some relation to most cases.

SUMMARY

1 Attention is directed to the fact that convalescence from arthritis is frequently characterized by a reduction of soft tissue swelling, particularly evident though rarely conspicuous in the hands, and concurrent with a diminution of pain and increasing range of joint motion.

2 In a series of selected cases, approximate water balance estimations have indicated that a net loss of water from the body accompanies a subsidence of swelling of tissues, pain, and limitation of motion.

3 It is suggested that disturbances of water distribution in tissues constitute significant factors in the dynamic pathologic changes of the rheumatoid syndrome.

4 An attempt to evaluate the role of dietetic and other factors in this series of events has been made by studying the different phases contributing to the net result. The administration of several types of low calorie diets has been shown to be associated with a net loss of water and with clinical improvement.

5 Dehydrating diets, adequate in calories, high in protein, low in fluid and high in fat induced a net loss of water from arthritic patients with clinical evidence of improvement, and the suggestion is made that the relative in-

crease of fat and protein metabolized on low calorie diets exerts a significant influence in the striking clinical results frequently achieved

6 Recumbent rest is considered as acting, in part, by favorably influencing a shift of fluid from the tissues to the blood and lymph channels

7 Many seemingly unrelated factors which influence arthritis favorably when used within proper limits, such as dietetics, recumbent rest, heat and massage, may act in part by favoring fluid removal from tissues

8 Attention is directed to the fact that a negative water balance contributes to recovery from both atrophic and hypertrophic arthritis. This suggests that both types of arthritis arise, in part, from similar or comparable premises, and further, that rigid restriction of many therapeutic measures, especially those here mentioned, to one type alone is unwarranted

9 The relationships pointed out do not imply that dehydrating measures alone constitute a therapeutic escape from arthritis. Vigorous sweating, purgation or diuresis have long been known to be of only limited value, and even dangerous. So far as changes in the distribution of tissue fluids in arthritis may be desirable, they should be achieved by the more sustained and "physiological" influence and measures we have discussed

10 Further justification is afforded for the controlled use of dietetic measures in the treatment of arthritis. The reader is again cautioned as to the dangers involved in uncritical employment of this agency

The authors are indebted to Dr Theodore F Bach for assistance in clinical details and to Miss M Robinson for supplying data on the weights and composition of the foods consumed by the patients

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SOME OBSERVATIONS ON MERCURIAL DIURETICS¹

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THE use of mercury as a diuretic was advocated first by Jendrassik¹ in 1886. He administered frequent small doses of calomel by mouth and by this means obtained in many cases a marked increase in urine volume. Gradually this form of treatment fell into more or less disuse as observers reported deleterious effects as a result of the mercury absorbed. In recent years, following the introduction of the complex organic compound of mercury, novasurol, first described by Saxl and Heilig² in 1920, mercury has again assumed a prominent place in the treatment of edematous conditions. The favorable results which the above investigators reported have been abundantly confirmed. As with all complex drugs other similar combinations were sought which would produce, if possible, greater results with less toxicity. Although toxic symptoms from novasurol were comparatively rare it came to be replaced by salyrgan which also induced marked diuresis but with fewer toxic manifestations. The literature relating to both of these substances has been fully reviewed recently by Binger and Keith³ and by Schmitz⁴. In order to intensify the action of the mercurial diuretics efforts have been made to combine their use with other substances which were also known to produce an increase in urine volume. Keith, Barrier and Whelan⁵ noted very beneficial results as a result of a combination with ammonium chloride while more recently Herrmann and his co-workers⁶⁻⁸ have shown that theophylline and salyrgan given together induce a greater effect than the use of either alone. The former has been recognized as a potent diuretic since its action was described by Von Schroeder⁸. The latest mercurial diuretic introduced is one in which a complex mercurial salt is combined with theophylline⁷. The mercury content of this drug is essentially similar to that in novasurol and salyrgan. Excellent clinical results and a low incidence of toxicity have been reported by Hahn,⁹ Popper,¹⁰⁻¹¹ Saxl,¹² Spengler,¹³ and Pratsikas.¹⁴ The present investigation was undertaken to study the effect of this preparation and to observe whether it offered any advantages over those in common use.

METHOD OF INVESTIGATION

The patients on whom the observations were carried out remained at rest in bed. High carbohydrate diets were used and one gram of sodium chloride was given per diem. The daily fluid intake was restricted to 1200

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† Originally introduced as Novurit, this drug is sold in America under the name of Mercupurin.

c c In the cardiac cases the patients were fully digitalized before the mercurial diuretics were given and were continued on a maintenance dose throughout the period of observation. In most instances xanthine diuretics had been unsuccessfully used before commencing the mercurial group. In fact before the period of study, many had had fluid removed mechanically from the abdominal or thoracic cavities. Preparatory to the administration of the mercurial diuretics the urine volume in 24 hours was carefully measured until it remained practically steady for a period of at least three days.

The mercurial diuretics were used in doses of one to two c c intravenously in every instance. As a rule a preliminary injection of one c c was given to determine the possibility of an idiosyncrasy. Thereafter, as a rule the dose was two c c. Usually the injections were repeated at intervals of four days although in one case which showed a particularly good response only two days were allowed to elapse. The intake and output of fluids were carefully measured throughout the period of study. When the diuresis was prolonged beyond 24 hours the total for the following day minus the normal average output without the drug was included in the total diuretic response. Changes in weight were not followed as many of the patients were so sick that it was inadvisable to get them out of bed to weigh them. At frequent intervals, particularly on the day following injection, the urine was carefully studied for albumin and blood cells in order to be certain that renal injury was not produced. In many instances blood urea nitrogen estimations were also performed throughout the study. More injections of mercupurin were given than of salyrgan. The latter, however, was not administered after all the observations on the former had been made but spaced irregularly during the period of investigation.

RESULTS

Fifteen patients, all in advanced stages after long periods of invalidism, were studied. Ten suffered from heart disease and five from cirrhosis of the liver. They received a total of 118 injections of mercupurin and 20 of salyrgan. It was considered inadvisable when trying a new mercury preparation to use patients in whom any marked degree of kidney damage was present in view of the great liability of the kidney to injury by mercury.

In every instance the administration of the diuretic was followed by an increase in the output of urine, often to a very marked degree. The diuresis commenced as a rule within three hours and attained a maximum in about eight to 12 hours. Generally the effect passed off in 24 hours but sometimes it persisted during the following day. In no instance was it prolonged beyond this period. As had been noted by other observers, frequent repetition of the drug often tended to lessen the urine volume after later injections, even in those cases in which there was considerable edema fluid still present.

The results in individual cases both with mercupurin and salyrgan are presented in table 1. In each patient the maximum and minimum outputs

are given for different doses of a particular drug and also an average for all injections of the same dose. Figure 1 illustrates in each case the average

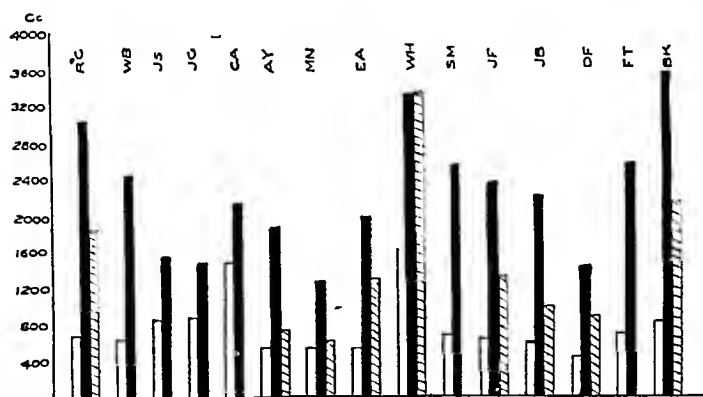


FIG 1 The average urine volume in the different cases following the administration of mercurial diuretics (Plain blocks—normal, solid blocks—mercurpurin, cross-hatching—salyrgan)

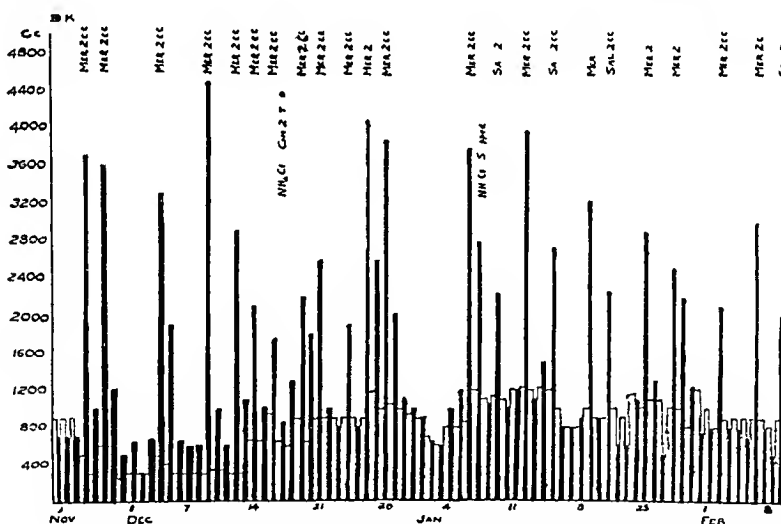


FIG 2 The response to the administration of mercurial diuretics throughout the period of study in case BK (Plain blocks—intake, solid blocks—output, Mer—mercurpurin, Sal—salyrgan)

urine volume without mercurial diuretics and that after mercurpurin and salyrgan. Figure 2 shows a case which responded particularly well to this type of diuretic. In every instance, except one, in which mercurpurin and salyrgan were compared, the response to the former was greater than to the latter. In some cases, during part of the period of observation ammonium chloride, gm 8 per diem, was given and generally there was some increase in the response both with mercurpurin and salyrgan.

TABLE I

Urine volume in c c during period of diuresis

| Case | Diagnosis | Average daily intake c c | Average daily output before drug c c | Urine volume in c c during period of diuresis | | | | | | | | | |
|------|---|--------------------------|--------------------------------------|---|--------------|--------------|--------------|--------------|-----------|--------------|------|------|--------------|
| | | | | Mercaptopurin | | | | | Sallyrgan | | | | |
| | | | | Dose c c | No of inject | Max | Min | Av | Dose c c | No of inject | Max | Min | Av |
| R C | Hypertensive heart disease | 800 | 700 | 1 2 | 1 2 | 4150 | 2100 | 1100 3125 | 2 | 1 | | | 1850 |
| A Y | Mitral stenosis Aortic insuff —rheumatic | 732 | 588 | 1 2 | 1 10 | 2700 | 1200 | 360 1861 | 1 2 | 1 1 | | | 840 660 |
| M N | Aortic insuff —luectic | 738 | 566 | 2 | 14 | 3212 | 500 | 1298 | 2 | 2 | 800 | 500 | 650 |
| E A | Mitral stenosis—rheumatic | 771 | 559 | 1 2 | 2 4 | 3141 2261 | 2221 1361 | 2681 1655 | 1 | 1 | | | 1320 |
| W H | Arterio sclerotic heart disease | 809 | 1638 | 1 2 | 2 2 | 4200 3762 | 3362 2000 | 3781 2881 | 2 | 2 | 3600 | 3100 | 3350 |
| S M | Arterio sclerotic heart disease | 1028 | 696 | 1 2 | 1 7 | 3100 | 1000 | 6500 2000 | | | | | |
| W B | Mitral stenosis—rheumatic | 900 | 750 | 2 | 6 | 3650 | 1300 | 2450 | | | | | |
| J S | Arterio sclerotic heart disease | 700 | 830 | 1 | 2 | 2200 | 950 | 1578 | | | | | |
| J G | Arterio sclerotic heart disease | 1150 | 900 | 1 2 | 1 1 | | | 1700 1300 | | | | | |
| C A | Mitral stenosis—rheumatic | 981 | 1509 | 2 | 4 | 2550 | 1650 | 2137 | | | | | |
| B K | Cirrhosis of liver | 820 | 820 | 2 | 20 | 5880 | 1750 | 3535 | 2 | 4 | 2750 | 2000 | 2332 |
| J F | Cirrhosis of liver | 979 | 682 | 1 2 | 1 4 | 3718 | 1050 | 3218 2159 | 1 2 | 1 3 | 1500 | 900 | 1950 1167 |
| J B | Cirrhosis of liver | 850 | 600 | 1 2 | 1 8 | 3400 | 1000 | 1500 2170 | 2 | 2 | 1400 | 600 | 1000 |
| D F | Cirrhosis of liver | 710 | 450 | 1 2 | 1 2 | 1800 | 850 | 550 1325 | 2 | 1 | | | 900 |
| F T | Cirrhosis of liver | 1028 | 696 | 1 2 | 1 7 | 3100 | 1000 | 6500 2000 | | | | | |

EVIDENCES OF CLINICAL IMPROVEMENT

In most instances there was striking improvement in the condition of the patient. R C, suffering from ascites and edema of the legs, was rendered edema free. A Y, who had extreme edema which had persisted for many months and had failed to respond to all forms of treatment including salyrgan, showed a marked reduction in the edema after mercupurin injections. Although abdominal paracentesis had previously to be performed at frequent intervals, this had only to be done once after this type of treatment was instituted. M N at first responded in a satisfactory manner but later failed to show any benefit. E A was rendered edema free and ascites disappeared. W H, prior to the use of mercurial diuretics, required the removal of fluid from either the pleural cavity or abdomen at weekly intervals but the injections produced such marked relief that after this treatment the chest had to be tapped on only one occasion and ascites did not reaccumulate. S M, who at the beginning of the study had edema of the legs, ascites and right hydrothorax, was rendered edema free. W B had massive edema of the extremities and marked ascites both of which were completely removed. J S suffered from marked ascites which was relieved on discharge. J G showed moderate edema which disappeared. C A had ascites and edema of the legs, both of which were absent after treatment. B K required abdominal paracentesis at weekly intervals before mercurials were used but thereafter only had one tapping in two and a half months. J F responded well to the drugs but died despite the relief of the ascites. J B had fluid removed from the abdomen at six to 12 day intervals over a period of three months but after the injections were instituted the ascites disappeared. D F did not give a satisfactory response and slowly accumulated fluid despite the use of any form of diuretic. F T required frequent abdominal paracentesis but after the use of mercurial diuretics this had not to be repeated.

EVIDENCES OF TOXICITY

In no case was there any reaction following the injection of either drug. The urine studies showed no evidence of renal damage while the blood urea, even in those cases in which it was slightly elevated, remained essentially the same after many injections had been given. A possible explanation of the lack of evidence of toxicity may be that no cases were used which showed marked renal involvement. Binger and Keith³ found that these were most likely to show toxic phenomena although such phenomena sometimes presented in patients with hepatic damage. The lowest incidence occurred in heart cases which constituted the majority of cases in our series.

DISCUSSION

The problem of diuresis is one which has been subjected to much investigation but the importance of the removal of edema fluid is such that

every effort should be made to improve the methods of dealing with a sign of such grave import. That the mercurial diuretics have proved a marked advance in this respect is unquestioned. Our results demonstrate that most satisfactory results were obtained by their use in almost every instance while evidences of toxicity were absent. All cases had received other forms of diuretics without any benefit and apparently offered a very bad prognosis. In several instances the administration of the mercurial preparations merely prolonged life for a period, but in many others the patients were returned to a life of some usefulness. Even in the former the symptomatic relief was very marked and the comfort of the patient materially increased.

A great deal of discussion has arisen as to the mode of action of the various forms of diuretics. As regards the mercurial diuretics it is agreed that changes in the circulation play no part. However, there is a divergence in the point of view as to whether the action is on the extra-renal tissues or on the kidney itself. In their original communication Saxl and Heilig² favored the former. Crawford and McIntosh,¹⁵ in their investigation, found that although there might be some evidence for this during a very short period after the drug was administered, it was unimportant compared to the renal effect. Many investigators have supported one or other viewpoint. The literature is fully reviewed by Schmitz⁴. Both the latter and Herrmann and his co-workers^{6, 7} have utilized the Rehberg method of calculating the amount of glomerular filtration and the amount of tubular reabsorption in the study of this problem. Each concluded that the mercurial diuretics act mainly by decreasing tubular reabsorption. In a later paper Schmitz¹⁶ stated that he found no evidence of extra-renal action. Lassen,^{17, 18} however, using a similar method obtained a decrease in glomerular filtration in normal individuals after salyrgan but an increase in cases of cardiac edema in which the initial value was low. Further evidence of a direct action on the kidney is furnished by the experiments of Bartram¹⁹ in which he injected salyrgan into one renal artery. With a small dose there was a diuresis from that kidney and none from the other.

The mode of action of the xanthine diuretics is similarly the subject of much discussion. Von Schroeder⁸ believed that it was independent of the circulation while another school considered that circulatory changes were the main factor. Others stated that the seat of action was the extra-renal tissues while another group believed that a renal effect was responsible. Even the latter disagreed as to whether the action was on the glomeruli or the tubules. This subject is fully discussed by Schmitz⁴. He, as well as Herrmann and his associates,^{6, 7} in the investigations referred to above, also studied the xanthine group. Both state that there was a marked increase in glomerular filtration while the changes in tubular reabsorption were slight and inconstant. Davenport, Fulton, Van Aiken, and Parsons²⁰ as a result of their studies on dogs conclude that the Rehberg method does not give an accurate index of glomerular filtration. Blumgart and his associates,²¹

using a modified Rehberg method, were unable to demonstrate any increase in the amount of glomerular filtrate with either euphyllin or salyrgan

A review of the literature at the moment seems to indicate that both the xanthine and mercurial diuretics have their main action on the kidney, the former increasing glomerular filtration and the latter retarding tubular reabsorption. However, further investigation must take place before final conclusions are made. Assuming that this view is correct, there appears to be a sound theoretical basis for the use of a combination of these two types of diuretic

CONCLUSIONS

1 A combination of an organic mercurial compound with theophylline has been investigated on a series of cases of advanced heart failure and cirrhosis of the liver. In every instance a satisfactory increase in urine volume was produced without toxic effects

2 This preparation was compared with the results of injecting an organic mercurial preparation alone, and in every instance except one the average diuresis was greater in the former

3 The theoretical advantages of such a combination are discussed

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CUTANEOUS TUBERCULOSIS AND GENERAL MEDICAL DIAGNOSIS *

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THE diseases of the skin which are recognized as bearing some relationship to tuberculosis have in recent years been so increased in number that the subject is now a complex one, and of great importance in its respect to general medical diagnosis.

The cutaneous disorders associated with tuberculosis are readily divisible into two groups. In the first are found those dermatoses which are universally accepted as due to the tubercle bacillus, and which show a pathological picture not differing materially from that seen in other organs of the body affected by tuberculosis. Lupus vulgaris, scrofuloderma, tuberculosis cutis orificialis and tuberculosis verrucosa cutis are included here. These disorders are as a rule generally recognized and their significance appreciated.

The second group is the one with which we are particularly concerned, as it consists of a large number of dermatoses whose relationship to tuberculosis is in some types definitely proved, and in others only doubtful.

Although for many years a number of dermatoses had been observed in which an association with tuberculosis had been suspected, it was not until 1896 that Darier placed in a single group these eruptions whose manifestations did not correspond at all to the picture of cutaneous tuberculosis seen in the members of the first group. He called attention to the fact that there existed a number of cutaneous disorders which occurred in individuals suffering with tuberculosis and which had a number of features in common, among these being a benign course, tendency to spontaneous cure, wide and symmetrical disposition, tendency to recurrence in successive crops without fever and a varied histological picture often suggestive of tuberculosis.

From time to time additions have been made to the list of tuberculides, until at present we have a group of some 25 disorders in which it has been suggested that a systemic tuberculosis is responsible for the eruption. In the case of four of these conditions, i.e., erythema induratum, lichen scrofulosorum, acnitis, and folliculitis, it is generally conceded that tuberculosis is responsible for the eruption, while with the other members of the group the evidence of such a relationship varies from almost conclusive to very slight.

As to the manner in which the systemic infection produces these disorders, there are various theories. They were at first thought to be due to the action of toxins elaborated by the tubercle bacillus in its primary focus and carried to the skin by the blood stream. Others felt that they were due to dead bacilli circulating in the blood, to the production of microbic emboli by organisms of low or attenuated virulence, or to a special filterable form.

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

of the bacillus. Avian and bovine types of organisms were also suggested as the responsible agents. In 1914 Rist and Rolland¹ contributed the theory which has gained widest acceptance. After extensive research, they concluded that the tuberculides occur in individuals who, as a result of a latent or manifest form of tuberculosis, have developed a state of allergy, the tuberculides thus representing the reaction of the sensitized skin to the tubercle bacilli carried to it by the blood stream from a visceral or other focus of infection. The tuberculide lesions therefore represent spontaneous examples of Koch's phenomenon resulting from endogenous inoculation of the skin, and the ensuing destruction of the bacteria accounts for the spontaneous healing as well as for the infrequency with which tubercle bacilli are found in the cutaneous lesions. This theory is supported by the fact that the bacilli can be demonstrated much more frequently in very early lesions, i.e., those in which the allergic reaction has not developed to the point of destruction of the organisms, are selected for examination. Wise has summarized this by stating that the variations in form and type of eruptions provoked by the tubercle bacillus seem to depend upon three factors: (1) the individual disposition of the patient, (2) the number of bacilli circulating in the blood stream, and (3) the degree of immunity reaction residing in the affected organism.

More recent than the above theory, but not generally accepted, is the idea that the tubercle bacillus presents in its life cycle a virus or a granular form, and that these forms of the organism are responsible for the development of tuberculides.

A number of writers have called attention to the diagnostic importance of those members of the tuberculide group which are generally accepted as being due to tuberculosis, and to the fact that the physician all too frequently fails to recognize their significance. The presence of an eruption of lichen scrofulosorum, papulo-necrotic tuberculides (acutis and folliclis) or erythema induratum, if properly diagnosed, should instigate a search which will frequently disclose an unsuspected focus of tuberculosis, most often in the lymph glands, but at times in bones, joints, the intestines or other parts. Active tuberculosis of the lungs is infrequent with these disorders. At times, as Goeckerman² has pointed out, they are of value in disclosing the source of disturbance in cases where the symptoms are obscure, where only the presence of tuberculides may suggest the source of frequent headache, malaise, vague pains, asthenia, lack of endurance and obscure fever. Their presence is taken to indicate an active though chronic tuberculous infection which gives rise to periodic attacks of bacillemia, resulting in the formation of embolic obstruction of the vessels of the skin and subcutaneous tissue.

As evidence of the frequency with which the value of these eruptions is overlooked may be cited the observation of Stokes,³ who found that in only five of his cases of papulo-necrotic tuberculide had a correct diagnosis been made, and 57 per cent of the cases showed incontrovertible objective evidence of tuberculosis and 13 per cent had disputable signs, and that of Hayes,⁴

who reported three cases of the same type, two of them in patients with active pulmonary tuberculosis, and pointed out that each of the patients had been seen by a number of physicians whose work was devoted largely to tuberculosis, and the lesions diagnosed as anything from simple dermatitis to syphilis and leprosy.

It is impossible to consider all the other and less well established members of the group of tuberculides, but in the case of three of the disputed ones, erythema nodosum, erythema multiforme and the sarcoids, developments of recent years have been of interest.

With regard to erythema nodosum and a possible tuberculous etiology, interest has been widespread in the last few years only, although Willan in 1798 was probably the first to remark upon the connection of these two diseases, when he noticed that tuberculosis occasionally followed an attack of this eruption. Uffelmann⁵ in 1876 and Poncet⁶ in 1902 were other early observers of this association. Pons⁷ in 1905 showed giant cells in sections of a nodule of erythema nodosum and also called attention to the development of typical nodules in an individual after a diagnostic dose of tuberculin. Brian produced tuberculosis in three guinea pigs by injecting blood from a patient who had erythema nodosum, but who had no clinically recognizable tuberculosis. Landouzy⁸ described erythema nodosum as a complication in a case of tuberculosis septicemia, and another case of the same disorder in which he was able to find a single acid fast bacillus in the lumen of a vessel in one of the lesions, and inoculation of a guinea pig gave positive results.

In 1912 Pollak⁹ reported a study of 42 cases seen during a two year period. Although the patients ranged in age from one to 13 years, so that tuberculosis would not be expected frequently, all gave positive reactions to tuberculin. The tests were still positive months later, and in three of the cases definite tuberculosis developed within three to 10 months, while others showed evidence of phlyctenules and tuberculosis of the bones.

Ernberg¹⁰ saw 35 children with erythema nodosum between 1908 and 1914, and was able to examine personally 31 of these patients during 1916 and 1917. Not one of the patients had developed any signs of rheumatism, but 13 showed symptoms of tuberculosis and one had died of miliary tuberculosis.

Vetlesen,¹¹ who regards erythema nodosum as a danger signal, found that 5.1 per cent of his patients with pleurisy had previously had erythema nodosum, as had 0.9 per cent of the patients with other manifestations of tuberculosis. Symes¹² found that 10 per cent of his cases of erythema nodosum showed tuberculous disease within six months, and in a later report recorded three more cases of erythema nodosum, in two of which tuberculosis developed later.

In spite of strong evidence of an association between erythema nodosum and tuberculosis shown by these and numerous other observations, the findings could not be considered conclusive. Symes stated that "There is an undeniable association between erythema nodosum and tuberculosis. The

evidence in support of this fact is strong on the clinical side. Tuberculin tests and skiagraphy in the hands of experts afford confirmatory evidence of high value. The pathological and bacteriological evidence is weak." Wallgren¹³ has added valuable support in the latter field, in reporting on the results of examination of the stomach washings by the method of Meunier in 40 children suffering with erythema nodosum. Thirty-seven of these reacted positively to tuberculin, and in 17 of these tubercle bacilli were found after guinea pig inoculation. Collis confirmed this in three out of five tuberculin positive cases.

Dickey¹⁴ in 1932 found 100 per cent of 16 patients under 15 years of age with erythema nodosum to have positive tuberculin reactions. The majority of his patients were girls, and all the patients gave positive reactions to tuberculin and most of them to minimal doses. In four of them the rash followed the use of tuberculin. In most of the cases a perifocal reaction was demonstrated by roentgen-ray examination.

Saenz et al¹⁵ recently reported the case of a woman aged 30 years who developed erythema nodosum. The tuberculin reaction was positive and a tracheo-bronchial adenopathy was shown by roentgen-ray examination. He injected the sediment of centrifuged blood taken from the patient into guinea pigs. Both of these died of intercurrent infections, but showed gland involvement with numerous acid fast bacilli present. Material from these glands produced generalized tuberculosis in guinea pigs. Material from one of the skin lesions was injected into four guinea pigs. Only two survived. Of these, one showed no signs of tuberculosis, but the other developed enlarged glands in which only a few acid fast bacilli were found. Material from these glands injected in other guinea pigs produced large caseating glands with numerous bacilli present. The authors interpret these findings as indicating that even with a profuse bacillema the organisms in the skin lesion are few in number, thus explaining the difficulty of demonstrating them in sections.

Wallgren¹⁶ has reported an observation of 36 girls of about 10 years of age in a single classroom, 18 of whom had erythema nodosum. Later all of these so affected gave positive Pirquet reactions and 13 had changes about the hilum demonstrable by roentgen-ray, and four others showed definite changes. He found an open case of tuberculosis in one of the girls in the class, and regarded this as the source of infection.

Massini and Bale¹⁷ in 29 cases of erythema nodosum found tuberculous involvement in 14. Ernberg,¹⁸ reporting again in 1932, states that all of his investigations and those of other writers led him to believe that erythema nodosum can be explained as an autogenous tuberculin reaction. He feels with Wallgren that this cutaneous picture usually develops at an early stage of tuberculosis, appearing at a time which can be regarded as the end of the incubation period, i.e., the time at which the allergy to the disease becomes established as shown by the development of a positive reaction to ordinary doses of tuberculin. He regards erythema nodosum as a sign of

active tuberculosis, whether it appears thus at the transition between the preallergic and allergic states in a newly infected person, or in connection with an acute infectious disease or other agencies activating a previously existing tuberculosis

In the experience of most observers erythema nodosum is associated with a focus of tuberculosis in the region of the hilar glands, but the focus may be found in other areas

While not all writers are in accord as to the exact character of the relationship between tuberculosis and erythema nodosum, practically all who have studied the subject agree that such an association exists, particularly in erythema nodosum occurring in children. Symes, Wallgren and Ernberg, among others, urge that patients who have suffered erythema nodosum be allowed a long period of convalescence with open air treatment and extra feeding. It is urged that all children who have had erythema nodosum undergo a roentgen-ray examination for changes in the region of the hilum. The early detection of tuberculous involvement is not only of value to the child, but also by preventing his return to school will save other children from exposure to tuberculous infection.

It is not to be inferred that even in children erythema nodosum should be regarded as due to tuberculosis in every instance, as the same clinical picture may be caused by other infections, principally streptococcic, and by the ingestion of drugs.

There are, however, in many cases of tuberculous origin, certain clinical differences which may aid in the determination of the etiology. In the tuberculous variety the lesions are apt to occur in unusual locations, with a greater tendency to localize on the posterior aspects of the legs. The nodules are smaller, tend to be less numerous, and the inflammatory reaction is less acute. The process as a whole is less active, the lesions being less tender and more persistent, at times lasting for some months. In rare instances these persistent lesions may change in type and present the classic picture of erythema induratum, even going on to ulceration.

With regard to tuberculosis as a cause of erythema multiforme, the evidence is much less abundant and not as convincing. The possibility of a causative relationship here was probably considered largely because of the recognized association of erythema nodosum and erythema multiforme. Ramel¹⁰ of Lausanne has been the chief proponent of this idea. He is convinced of the tuberculous nature of lupus erythematosus, and because of a clinical relationship seen at times between this disorder and erythema multiforme was led to seek a common etiology, particularly after he had seen papulo-necrotic tuberculides appearing on the fading lesions of an eruption of erythema multiforme. In an exhaustive report, Ramel stated that in eight cases of erythema multiforme he was able to demonstrate Koch's bacillus in the blood of all the patients and in the lesions of two of them, while in a later report the number of cases was increased to twenty-one. None of the patients presented traces of active tuberculous infection and

none gave a history of previous infection. He states that the type of tuberculosis is peculiar in that it can only be demonstrated by inoculation of guinea pigs. In the first inoculation no typical changes are produced in the animal. By successive inoculation of material taken from this and succeeding animals, a typical inoculation tuberculosis is secured, with a gradual appearance of acid fast bacilli in conjunction with the increase in the virulence of the infection. He believes that his method demonstrates that in the guinea pig there can exist a benign tuberculosis, characterized by non-follicular lesions, and that a tuberculous virus which can determine this type of infection in the guinea pig is present in the blood of patients suffering from erythema multiforme who do not present any clinical manifestation of tuberculosis as usually interpreted. The classic erythema multiforme of Hebra is interpreted by Ramel therefore as a non-follicular type of tuberculous manifestation, of hematogenous origin.

Percival and Gibson²⁰ and Hallam and Edington²¹ have each investigated 10 cases of erythema multiforme, duplicating the method of Ramel, and in none of the 20 has it been possible to duplicate his findings.

It can only be said on the basis of the evidence thus far brought forth that the idea that erythema multiforme is of tuberculous etiology has not been established, but infection with tubercle bacillus must nevertheless be regarded as a possible cause in a certain proportion of the cases of this disorder which is generally looked upon as a complex of varied etiology. Stokes³ includes this disorder with erythema nodosum and purpura as diseases which are of great diagnostic and prognostic significance in regard to tuberculosis.

With regard to the sarcoids, Boeck and Darier, who originally described the two types known respectively as benigniliary lupoid or multiple benign sarcoid and the subcutaneous sarcoid of Darier-Roussy, believed the disorder to be of tuberculous origin, but this view is not universally accepted at present, although the majority of observers support the idea, and many are willing to accept these lesions as proved tuberculides. The opposition to this view is in part due to the fact that syphilis, leprosy and other disorders may produce lesions which may resemble the sarcoid and which may be wrongly included under this heading. Opponents of the tuberculous theory point out the infrequency with which tubercle bacilli are found in the lesions and the usual negative results of inoculation of tissue into guinea pigs in support of their opinion, but Kyrle, who believes that the lesions of sarcoid represent a foreign body reaction to the tubercle bacillus and its disintegration products, has shown that the organisms are present only in the very early lesions, which have not as yet developed the characteristic histopathologic picture as the allergic reaction rapidly destroys them, thus accounting for the failure to demonstrate the organism in the fully developed lesion and for the failure of inoculation experiments.

The tuberculin test is almost always negative in patients with sarcoid, but Jadassohn and others have explained that in this group, in contradistinc-

tion to the hyperergic state which exists in the case of other types of tuberculides, the allergy has progressed almost to the state of desensitization, resulting in a condition of hypoergy or even anergy

One of the most interesting aspects of the sarcoids is the frequency with which the skin lesions are associated with changes in other parts of the body, principally nodular infiltrations of the lungs, fibrocystic changes in the bones (especially in connection with the lupus pernio type of lesion), splenomegaly and adenopathy. Since these systemic changes in conjunction with sarcoids were first described, more careful observation has shown one or more of them to be demonstrable in a considerable proportion of cases

SUMMARY AND CONCLUSIONS

The proved tuberculides, lichen scrofulosorum, papulo-necrotic tuberculides and erythema induratum, disorders of relatively frequent occurrence, furnish diagnostic and prognostic indices in tuberculosis which are often not diagnosed or appreciated. Their presence usually indicates an active though usually chronic form of tuberculosis most often involving the glands, bones and joints. Their presence indicates a high degree of resistance to the tuberculous infection, and therefore the prognosis as to the course of the latter is usually good.

Erythema nodosum, while undoubtedly a disease of complex etiology, is in some instances, and particularly in children, due to infection with tuberculosis. It tends to occur early in the course of the latter disease, and should indicate the advisability of insisting upon a prolonged convalescence and careful observation for a period of at least six months.

Erythema multiforme has not been established as a tuberculide, but there is evidence sufficiently suggestive to indicate that tuberculous infection may be responsible for a small proportion of cases.

The evidence would indicate that the sarcoids, together with the changes found frequently in other structures, can best be accounted for on a tuberculous basis.

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ATYPICAL HAY FEVER SEASONS, THEIR SIGNIFICANCE IN TREATMENT *

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IT is now an accepted fact that specific and successful treatment of the hay fever patient presupposes a careful botanical investigation of the district in which the sufferer resides. Because of the marked variations in the flora of various parts of the country it has been necessary to make extended studies in many localities. While it cannot be said that the data which are at present available are entirely complete, nevertheless, we have information as to hay fever plants and pollen distribution in many representative sections of the country. The means used in surveying any locality consist of field observation and analyses.¹ Field excursions conducted at various seasons of the year tell us of the kinds and quantity of probable hay fever plants and their seasons of pollination. The investigation of the air tells us the types of pollen capable of being transported by the wind, the scarcity or abundance of such pollens and the season for each particular variety of pollen.

The hay fever situation in any individual community has had to be studied further by observations on patients. Clinical tests have shown us that certain pollens, such as pine, although they may be present in the air in large numbers, fail to produce symptoms. Certain groups of plants characteristically produce very mild symptoms, certain others are well recognized as producing violent symptoms. The importance of some pollen-producing plants in some communities has been unduly minimized because of the small amount of pollen they have produced, or because of the almost complete absence of hay fever during their period of bloom.

ANGER OF STANDARDIZED ETIOLOGY

The correlation of the clinical and botanical data in any community has given us a rounded study upon which to formulate our ideas bearing on the causation and treatment of hay fever there. As a result of such studies in various localities there has naturally resulted the standardization of our etiologic and therapeutic concept in many places.

Increasing experience has taught us that in any locality such standardization even though based on the average data obtained over a number of years of observation, may fail in unusual seasons. Unusual weather conditions may change the relative severity of the seasons and transform a plant ordinarily regarded as harmless into an important cause of hay fever. Of necessity it follows that if our treatment has been based entirely on the

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standard season we may be caught unawares and our therapeutic results will in some instances be disappointing. It is with the above idea in mind that we wish to call attention to the importance of considering in the management of our hay fever patient not only what the usual, but also what the atypical or unexpected season, may bring.

The 1934 hay fever season was atypical in many respects and in many parts of the country. We shall discuss somewhat in detail the unusual features of that season, particularly as it relates to the North Central states, and more specifically on data as gathered in Chicago and vicinity. It must be emphasized here again, however, that it is not our purpose to describe any local situation for the benefit of those locally interested but rather to illustrate some of the possible modifications which any year may bring in any place.

TYPICAL SEASON IN THE CHICAGO AREA

In the Chicago area, as in most parts of the North Central states,² especially east of the one hundredth meridian, there are three definite well-marked hay fever seasons caused by the pollens of the various trees, grasses, and the ragweeds. Tree pollens begin to appear in the air in quantity about the first of April and continue through May. The total amount of tree pollen in the air at any one time is not usually very great. Those trees which furnish the most of the pollen are oak, elm, poplar, the various maples, walnut and hickory. In spite of the fact that positive skin tests to tree pollens occur in a large percentage only a few persons have hay fever symptoms during April and the first part of May, and these are often interpreted as minor colds.³

The grass season begins in Chicago about the last week of May and lasts until the middle of July. The amount of grass pollen in the air during this time is never very great. This is probably due to the fact that grass pollens are all comparatively heavy. As a rule grass pollen is found to be much more toxic than any of the tree pollens, and a considerable number of people are sensitive to grass pollen only. Occasionally the symptoms are as severe as are ragweed hay fever symptoms.

Fall hay fever in Chicago appears any time after the first of August and continues through September. It is usually due to the pollen of ragweeds. Most persons who are sensitive to ragweed suffer severely unless protected by pollen treatment. The pollen content of the air as measured in the residence and business sections of Chicago during August and September is usually about 98 per cent ragweed, so that very little attention is ordinarily given to such possible offenders as Russian thistle, pigweed and lamb's quarters.

AN UNUSUAL SEASON IN CHICAGO

During April and May 1934, the pollen content of the air was unusually high in the Chicago district. It seems reasonable to attribute the unusual amount of pollen from oaks, cottonwoods, elms, walnuts and other trees to

the ideal weather conditions during the pollinating season. Usually the pollination of the trees is much interrupted by frequent rains, each of which, of course, washes the pollen out of the air and interferes with that being matured on the trees. The hot dry weather this spring favored the ripening of pollen as well as its distribution. At this time the drought had not become severe enough to affect vegetation as deeply rooted as are the trees. Many patients who in past seasons had had very mild or no symptoms during the tree season but who showed skin sensitiveness to tree pollens, had definite and severe symptoms of hay fever this year.

TABLE I
Pollen Content of the Air in Chicago for Two Seasons

| | 1933 | 1934 |
|--------------------|------|-------|
| <i>Trees</i> | | |
| Maple | 21 | 16 |
| Elm | 82 | 189 |
| Oak | 593 | 1078 |
| Hazel | 22 | 4 |
| Alder | 21 | 32 |
| Pine | 125 | 228 |
| Poplar | 44 | 41 |
| Walnut and Hickory | 35 | 145 |
| Birch | 24 | 148 |
| Linden | 2 | 2 |
| Sycamore | | 18 |
| Ash | | 12 |
| Ailanthus | | 2 |
| Willow | | 24 |
| Hornbeam | | 2 |
| Misc | 126 | 159 |
| | 1095 | 2100 |
| <i>Grass</i> | | |
| All species | 370 | 82 |
| <i>Weeds</i> | | |
| Red Sorrel | 49 | 46 |
| Chenopod | 108 | 341 |
| Composite | 4 | 3 |
| Hemp | | 2 |
| Ragweed | 7249 | 8625 |
| Misc | 72 | 91 |
| | 7482 | 9108 |
| Grand Total | 8947 | 11290 |

Table 1 shows the marked increase in tree and chenopod pollens in Chicago during the 1934 season. The grass pollen production was reduced to a fraction of the average. The ragweed pollen count was unusually high.

The effect of dry weather on the grass pollen crop was just the opposite of that on the tree pollen crop. Grasses, on account of their shallow root system, respond very quickly to varying amounts of moisture. It is easy to see the beneficial effect of even a moderate shower when the grass is withered and dry. Thus, after a long period of dry weather, such as we had this spring, grasses are much damaged, and consequently, can mature only a small quantity of pollen. The total amount of grass pollen recorded in the

"loop" district of Chicago this spring was less than 15 per cent of what it has been for any of the previous three years. Grass hay fever was a rare affliction this season.

Evidently, the drought favored the growth of plants which thrive on less moisture than our common Chicago weeds. Russian thistle, lamb's quarters and other members of the goosefoot family broadcast three times as much pollen as usual. These plants have always been present in fair abundance in Chicago.³ In some districts where the soil is favorable, Russian thistle is more common than any other weed. Some Chicago patients have given slight skin reactions and occasionally there has been a strong reaction to members of this family, but because of the relatively small output of pollen of this type, these reactions were seldom taken into consideration in therapy. This season, a number of patients began to have severe symptoms before ragweeds began to pollinate. On investigation it was found that these people were sensitive to Russian thistle and other chenopods and definite contact could be proved. The peak of the chenopod season occurred about nine days prior to the ragweed peak and it was not difficult to analyze the effect produced by the chenopods on the patients unprotected to it in spite of the fact that they were sensitive to both groups of pollens and that the two seasons overlap.

THE RAGWEED SEASON

In general, past experience seems to indicate that dry weather in June and July so retards ragweed development that the ragweed pollen crop may be predicted on much the same basis as a corn crop. On account of the drought this season, we felt confident that the fall hay fever season would be much less severe than usual, probably comparable to that of the drought year of 1930. Chicago had almost no rain during July, so on August 1 the giant ragweeds, then beginning to pollinate, were much below par, and short ragweeds were in many cases only a few inches high. One could hardly believe that rains beginning as late as the first week of August could so rejuvenate these stunted weeds that they would produce a normal crop. Giant ragweeds did not attain their usual growth but short ragweed responded like magic and, by the first week of September, was growing luxuriantly and producing abundantly.

Mild hay fever symptoms from ragweed began rather early, with severe symptoms occurring in most untreated cases by August 19. Counts on downtown slides as well as those exposed in the residence sections showed the apex of pollen contamination on September 4, which was the worst pollen day in Chicago since pollen record has been taken. The slide on the Post Office showed 1006 ragweed pollen per cubic yard. Severe concentrations continued until September 15 and toxic concentrations for another week. The total pollen count for the season was almost 20 per cent more than last year, and 70 per cent more than the average for the previous five seasons. Data from other parts of Illinois seem to show similar unusual

findings as were obtained in Chicago with respect to the pollens of trees, grasses, chenopods and ragweeds.

Frequent cool days resulted in many instances in a persistent nasal congestion, apparently due to a subacute inflammatory process, with resultant nasal obstruction but very little irritation, such as is shown by itching and sneezing. Sensitiveness to cold seemed to play a part in these patients. This has been observed in other seasons but, because of the cool days, has been more prominent this fall. Caution should be observed in advising hay fever patients to go to very cool places, refrigerators or on the water.

The rather frequent weather changes resulted in severe instances of asthma. It has been observed for a long time that the advent of asthma during the hay fever season is dependent on weather conditions more than on the pollen concentration.¹ Extreme weather changes such as rains, electrical storms, marked drops in temperature and marked barometric disturbances are prone to bring on attacks of asthma while the hay fever may be relieved. During the 1924 ragweed season we experienced an unusual amount of "bad weather"—many rainy days and frequent and great temperature fluctuations with the result that this season was one of the worst from the standpoint of asthma.

COMMENT

Apparently the standardization of what is usual for pollen production and hay fever symptoms in any locality may be disturbed by unusual weather conditions. The events in the Chicago area during the 1934 season would indicate to us that positive skin tests to tree and chenopod pollens (Russian thistle, lamb's quarters) should lead us to consider seriously treatment with such pollens in spite of the fact that the individual patient has usually had only minor symptoms caused by them. If such preseasonal treatment is not undertaken we should at least be ready to give coseasonal treatment with the appropriate pollen as soon as symptoms arise. The lesson to be learned applies, of course, to any district where the minor pollens are seldom considered in the treatment.

Another lesson to be learned from the above data is that prediction of the severity or date of onset of any part of the hay fever season is an extremely hazardous procedure, even if backed by many years of experience in the botany of hay fever. And finally, the recorded data of this year emphasize more than ever the importance of local botanical surveys and particularly the importance of counting and recording the varieties and amounts of atmospheric pollen for every day during every season.

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SENSORY CHANGES AND THE REFLEXES IN JUVENILE PARETIC NEUROSYPHILIS *

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BOTH the sensory changes and the reflex findings are of major diagnostic importance in juvenile paretic neurosyphilis. The present study, the fifth of a series of clinical studies of this disease, is concerned with the sensory changes including headaches, the status of the tendon and pathological reflexes, the temperature disturbances and the trophic changes in this disease. It is based on 43 personally studied cases and 610 cases reported in the literature.

SENSORY DISTURBANCES

Sensory disturbances in some form occur in juvenile general paresis in about 25 per cent of the cases, either as sensory skin changes, headaches, or leg pains. Their occurrence as reported in the 653 cases reviewed is as follows:

| | | |
|---------------|----------|---------------|
| Headaches | 74 cases | 11.3 per cent |
| Leg pains | 12 " | 1.8 " |
| Paresthesia | 9 " | 1.4 " |
| Hyperesthesia | 26 " | 3.9 " |
| Hypesthesia | 53 " | 8.1 " |

Headaches Some form of headache occurring subsequent to the onset of the disease is reported in 11.3 per cent of the cases. Headache occurred in only four of my 43 cases (9.3 per cent). It has been previously stated that in some cases an acute severe headache appears as an epileptic equivalent, and in a few cases it is reported as following an epileptiform attack. The headache varies as to type, location, severity and duration. It is mentioned as a frequent prodromal symptom (Dahl²) and special notice is taken of headaches by Peterson,¹¹ in whose case they had been severe five months prior to other general symptoms.

Leg Pains Cramp-like or lancinating pains in the legs are specifically mentioned only in 12 cases (1.8 per cent). Stewart¹⁷ has emphasized the fact that although many cases of juvenile paresis present tabetic signs, there is a very infrequent occurrence of the leg pains so common to the acquired form of the disease and quite frequently found in juvenile (congenital) tabes. They were not present in any of my cases, though often commented on by other authors. Arsimoles and Halberstadt¹ specially mention them, Koster⁸ found special interest in the lancinating pains in his case, and they are recorded as present in cases reported by Alzheimer²² (1895), Louvier²² (1907), Trapet²² (1909), Jelliffe²² (1913), Schlicht¹³ (1915), Klessens²² (1917), Kupffender²² (1918), Klemeberger²² (1918), Fischer²² (1921), and Masten²² (1929).

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It is of special interest to find that of these 12 cases, five presented exaggerated knee jerks, in four they were absent, in two they were normal, and in the other their status is not stated. Thus the possible association of these pains with tabes is at least confusing in all but the cases showing absent knee jerks.

Paresthesia, Hyperesthesia and Hypesthesia Paresthesia is recorded in only nine cases, hyperesthesia in 26 cases (3.9 per cent), and hypesthesia in 53 cases (8.1 per cent). Schmidt-Kraepelin¹⁴ reports six cases with regional hyperesthesia and 10 with hypesthesia. Weygandt²¹ and Sanger¹² both mention a sensory disturbance in their cases, and Soukhanoff¹⁶ reports an anesthesia present during labor. Halben's⁹ case was a tabo-paetic.

As Kraepelin⁹ points out, hypalgia appears always sooner or later in the acquired type of paresis. In the juvenile type because of the mental state it is often impossible to determine the presence of sensory changes accurately or even approximately. In some cases, the patient seems to be anesthetic, one of my patients repeatedly mutilated himself with sharp instruments and once clung to the radiator until his hands were severely burned (Case 2).¹⁰ To interpret such action as hypesthesia might be justified, and yet it is not conclusive evidence of paetic sensory change. On the other hand, certain cases (particularly the far advanced cases with contractures) seemed invariably hypersensitive, even to gentle stimuli, which again is no conclusive evidence of hyperesthesia. Consequently, it seemed impossible in my own series to draw any accurate conclusions about sensory changes.

CHANGES IN REFLEXES

The status of one or more of the tendon reflexes was recorded in 531 of the 653 cases. Notation was also made of the cases in which a Babinski sign, clonus, Romberg's sign, and sphincter disturbances were present. The incidence of these is shown in the following table.

| Reflex | Cases | Per cent of 653 Cases |
|-----------------------------------|-------|--------------------------|
| Arm reflexes (biceps and triceps) | | |
| Hyperactive | 141 | 21.5 |
| Normal | 29 | 4.4 |
| Diminished | 3 | .4 |
| Absent | 13 | 2.0 |
| Knee jerks (quadriceps) | | |
| Hyperactive | 416 | 63.7 |
| Normal | 34 | 5.2 |
| Diminished | 19 | 2.9 |
| Absent | 62 | 9.4 |
| Ankle jerk (gastrocnemius) | | |
| Hyperactive | 167 | 25.5 |
| Normal | 33 | 5.0 |
| Diminished | 13 | 2.0 |
| Absent | 35 | 5.3 |
| Babinski sign present | 97 | 13.7 |
| Clonus (ankle) | 74 | 11.3 |
| Romberg sign present | 44 | 7.7 |
| Sphincter control disturbance | 119 | 18.2 |

Tendon Reflexes The table shows the frequency, as reported, of the hyperactive, normal, diminished, and absent tendon reflexes for the arm, knee jerk, and ankle jerk. The data regarding the status of the reflexes in the arm are sufficient only to note that an increase of these reflexes is the general rule.

Information regarding the status of the knee jerks is given in 531 cases. If the percentage of incidence of the various responses is based on these cases, we find that this reflex is increased in 78.3 per cent, normal in 6.4 per cent, diminished in 3.7 per cent, and absent in 11.6 per cent. The incidence in my own series of 43 cases is very similar: 81.4 per cent increased, 9.3 per cent normal, 4.6 per cent diminished, and 11.6 per cent absent. (These figures add to more than 100 per cent since in three cases the response was unilateral and was counted under both responses. In these three cases, it was absent on one knee while the other knee gave a normal response in one instance, and hyperactive in the other two.)

The results of other investigators closely parallel these figures. Dahl² found the knee jerks increased in 86 of 112 cases (76.8 per cent), Schmidt-Kraepelin¹⁴ reports 90 per cent hyperactive and 7.5 per cent absent, Ferguson and Critchley⁴ found 100 per cent (of 16 cases) hyperactive, Klauder and Solomon⁷ report them present in "almost all the cases, but absent in a few."

As compared to the findings in the adult type of paresis (acquired), juvenile paresis shows a much higher frequency of exaggerated reflexes. Schmidt-Kraepelin¹⁴ quotes Fierz, who compiled his figures from 4,000 adults, as finding the knee jerk normal in 24.6 per cent, increased in 47.3 per cent, and absent in 28.1 per cent. Kraepelin⁹ states that they are increased in two-thirds of the cases. Junius and Arndt⁶ reported on the knee jerks in 992 cases, 16.3 per cent were normal, 54 per cent increased, and 29.6 per cent were diminished or absent.

Absent knee jerks were the finding in 11.6 per cent of cases (62 instances). This is a significant feature of juvenile paresis indicating posterior column involvement and the consequent association of the disease with tabes. Spinal cord involvement has been stressed by Junius and Arndt⁶ in acquired paresis (they noted it in 29.6 per cent of their cases), and by Torkel¹⁸ who found it in 16 per cent of 402 cases. Consequently we must conclude that 11.6 per cent of these cases reported as juvenile paresis, should be classed on the basis of their pathologic lesions as tabo-paresis. The inclusion of these cases as juvenile paresis is justifiable, however, since so far as can be determined, the other symptoms and signs predominately are paretic rather than tabetic. For the sake of pathological accuracy, Ferguson and Critchley⁴ in their study of congenital neurosyphilis presented a separate group of tabo-paresis, including 12 cases, seven of which were so classified only because they showed absent knee jerks. As is shown in the present large series of cases, as well as in adult paresis, a small number persistently do show a late secondary involvement of the posterior columns of the cord.

Normal reflexes are of special interest and are reported here as occurring in 64 per cent of the 531 cases with the status of the knee jerks known. Schmidt-Kraepelin¹⁴ found only one case in her 40 and there were three in my series and one additional which had a normal response on one knee and none on the other. The following case is of special interest, not only because the patient had normal knee jerks, but also was essentially negative on neurological examination. (It is very similar to the case reported by Toulouse and Marchand¹⁹ with normal pupils and reflexes, and with typically parietic post-mortem findings.)

*Case 15** The patient was a negro, aged 17. His father was excessively alcoholic, and the mother was reported to be well, but none of the family were available for investigation. He did not walk or talk until his third year. He progressed in school to the sixth grade, and became employed as a grocery messenger after that time. He was committed to us after arrest on complaint of his employer because the boy claimed to have been robbed while taking money to a bank. *Physically* he was underdeveloped with hypoplasia of the genitals. *Neurologically* on admission he showed normal pupils and reflexes, without gait disturbance or cranial nerve lesions. *Stigmata* besides his underdeveloped genitals, included a highly arched palate. *Mentally* he was childish, with very meager intellectual content, though oriented and coherent. He said he often heard God talking to him, but never gave details. Simple mental tests showed him entirely inadequate to give correct answers and often to even understand the questions. Basic mental age was five years. *Laboratory* The blood and spinal fluid Wassermann tests were positive. *Course* He was treated with mercury and after a temporary slight improvement was paroled for a short time, but returned. He developed marked paresis with ataxia and had to be confined to bed. He developed a marked tremor of his lips and tongue, and ataxic speech. No note was made at this stage as to the status of the pupils or reflexes, but with the spastic state, it is presumed they would have been increased. He deteriorated mentally, grew extremely weak, and died of an intercurrent infection at 19 years. The duration of symptoms was indefinitely estimated at two and a half years. No autopsy was obtained.

The ankle jerks in juvenile paresis are also generally increased, as indicated in the previous table, they are reported so in 25.5 per cent of the cases. In 35 cases (5.3 per cent) they were absent, and in these 35 cases, the knee jerks were hyperactive in seven cases, normal in one, and absent in the remaining 27 cases.

Babinski Sign (Dorsal Flexion of the Great Toe) The Babinski sign was present in 97, or 13.7 per cent, of the cases. Fairbanks³ mentions that "they are occasionally elicited but are uncommon" (referring also to clonus), whereas the Babinski sign was present in 25.6 per cent of my own cases, and in 40 per cent of Schmidt-Kraepelin's¹⁴ cases. Sehlleht¹³ and Kraepelin⁹ also mention its frequent occurrence. Occasionally, there is a more or less permanent dorsal flexion of the big toe, a phenomenon often seen normally in infancy. The high incidence of the Babinski may also in some way be linked with its frequent occurrence in infancy and early childhood. There are no figures regarding its occurrence in adult paresis, but it is certainly less common than in the juvenile type.

* Cases 1 to 14 are included in the other papers of this series.

Clonus Ankle clonus is reported as present in 74 cases (11.3 per cent). In my own series it was present in 11 cases (25.6 per cent), and was always associated with a marked spasticity and greatly exaggerated tendon reflexes. Schmidt-Kraepelin¹⁴ reports one case where clonus was present in the hand.

Romberg Sign This is reported present in 44 cases (7.7 per cent), although it was present in 20.9 per cent of my cases, all of which showed other evidences of ataxia. It was present in a fourth of the Schmidt-Kraepelin¹⁴ cases which showed ataxia (and approximately half of mine). Fairbanks³ makes the blunt statement that the Romberg sign "does not occur in this disease, at least in the child," which is certainly not in keeping with the facts just cited.

Sphincter Control The loss of sphincter control is difficult to judge, since the patient often reaches the mental state when no attention is given to sphincter control, and as a consequence it is recorded as lost. Probably the actual nervous regulation of the sphincters rarely becomes disturbed, except with marked spinal cord involvement. Disturbance of sphincter control is reported in 119 cases in the entire series of 653 cases (18.2 per cent) and Ferguson and Critchley⁴ report it in 62 per cent. Seventeen of my patients (39.5 per cent) were untidy so far as control of the sphincter function, but in none of these was there conclusive evidence of sufficient spinal cord involvement to cause a loss of sphincter control. In all, it might be truly said there was a loss of conscious control through mental deterioration, i. e. a cerebral loss of control.

TEMPERATURE REGULATION

In none of my cases was there reported any conspicuous body temperature change except with an intercurrent infection just before death, or in association with extensive bed sores in bedridden patients with contractures. Schmidt-Kraepelin¹⁴ noted some temperature fluctuations beyond the explanation of the apparent body state, but no hypothermia prior to death, as reported by Voisin,²⁰ and repeatedly observed in the adult form of paresis (Kraepelin⁹). Hyperthermia is occasionally present (Dahl²) without apparent explanation to be found on examination.

TROPHIC CHANGES

Trophic disturbances were not reported or apparent in any of my cases except in terminal bedridden cases in which the ulcers seemed to appear very easily and were not prevented even by the utmost care. I find no reference to such ulcers in Schmidt-Kraepelin's¹⁴ report. Sebald¹⁵ reports alopecia occurring in a case, and in one of Dahl's² cases there was a large pigmented hairy area covering the right scapula which was regarded as a stigmata rather than as having any association with the parietic process.

BASOPHILIC ADENOMA OF THE PITUITARY, REPORT OF A CASE OF "PITUITARY HYPERTENSION," TERMINATING IN CEREBRAL APOPLEXY *

By BENJAMIN A. GOULEY, M D, *Philadelphia Pennsylvania*

BASOPHILIC adenoma of the pituitary gland was described many years ago,¹ but it remained of restricted interest even to pathologists, the majority of whom have had little or no experience with the lesion. It will probably be seen with greater frequency as a result of Cushing's description of a well-defined associated syndrome.² This notable contribution was soon supplemented by equally stimulating papers by the same author on the questions of posterior lobe activity and its relationship to hypertension.³ These and the studies of others⁴ have served to focus attention on the pituitary as a probable factor in the development of hypertensive disease, and to emphasize anew the important rôle of that gland as the "motor of the body."

The absence (until recently) of a clinical correlation has obscured the importance of the basophilic adenoma. An excellent monograph⁵ on the pituitary adenomata as late as 1925, dismissed the basophilic lesion with one line, stating that it was of no clinical importance. It is an intraglandular growth, situated in the anterior lobe. The few illustrations on record give one the impression that it is mostly situated anteriorly at or near the periphery (as it is in the following reported case), probably the result of the usual peripheral distribution of the basophilic cells. A curious and most important feature is that the adenoma is often so small that it escapes detection on gross examination and even on the routine histological inspection of one or two sections. It stands out in the stained section (hematoxylin-eosin) as a small, dark nodule, usually well circumscribed, but without definite encapsulation. The circumscription is caused by slight compression of the surrounding tissue, and in the instance here reported, by a rather prominent encircling lymphatic or sinusoidal network. Secondary nodules or a diffuse basophilic hyperplasia in the remainder of the anterior lobe may also be present. The adenoma is usually composed of large cells, often arranged in cords showing in a general way some resemblance to the normal disposition of the pituitary chromophile cells. Only in one instance has an invasive tendency been reported, degeneration into a definite basophilic carcinoma has never been noted.⁶

The writer wishes to add another case report of basophilic adenoma, a good example of the syndrome described by Cushing. Unfortunately, this patient was in the hospital less than three days. Death ensued before adequate clinical studies were completed. The writer did not see the patient in

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life, but her appearance on the necropsy table was so striking that a tentative diagnosis of basophilic adenoma of the pituitary was made and verified by histologic examination

CASE REPORT

M.F., a white woman, aged 37 years, was admitted October 26, 1933 to the Medical Ward of the Jewish Hospital, on the service of Dr Edwin Heller. During her evening meal, she suddenly felt dizzy, and gradually went into stupor. Examination in the hospital indicated a cerebral apoplexy involving the right internal capsule; she never recovered from coma. Eye examination revealed advanced hemorrhagic neuro-retinitis. The initial blood pressure reading was 220 systolic, 140 diastolic. It gradually fell to 100 systolic, 80 diastolic. The history obtained from the family was meager. The patient had attended the out-patient department of another hospital for one year, during which time she suffered headache and impaired vision, and was known to have had hypertension and diabetes, during the last month, the headache was intense. There had been no precordial pain, nor leg edema, but there was occasionally some dyspnea on exertion. She was unmarried, her menstrual history was unknown, the past medical history had apparently been uneventful.

Laboratory examinations were as follows. Urinalysis showed a specific gravity of 1.030, a light cloud of albumin, and no sugar. Granular and hyaline casts, and occasional erythrocytes were found. The blood count showed 4,600,000 erythrocytes, 20,100 leukocytes (86 per cent polymorphonuclear neutrophils), and 84 per cent hemoglobin. The blood sugar was 186 mg per 100 cc of blood, the blood urea nitrogen, 22 mg. The blood plasma CO_2 combining power was 60 per cent.

Death occurred on the third day of hospitalization.

Necropsy. The body was that of a middle aged, white woman, of medium stature, obese, with large shoulders, large trunk, and marked abdominal enlargement, the forearms, wrists, and ankles were small and narrow. There was a marked overgrowth of hair over the face and upper lip, the forearms, the thighs, and legs, over the scalp it was black and lustrous. The breasts were of moderate size and firm in consistency.

The supporting tissues were moderately dehydrated, the fat deposits, especially in the abdomen, were greatly in excess.

The heart was hypertrophied and weighed 480 gm. No vascular or valvular lesions were noted. The kidneys were of normal size and presented the grayish, putty colored cortex ascribed to nephrosis, they showed surprisingly little fibrosis in view of the clinical history. The adrenals were moderately enlarged and although the medullae showed autolysis, the cortical tissue was definitely hyperplastic and contained increased lipid pigment. No adrenal tumor was noted. The thyroid was grossly normal. The ovaries were sclerotic and contained numerous small follicular cysts and a few corpora albicantes. The liver was grossly normal, but the pancreas appeared to be soft and presented numerous small foci of congestive softening in the body and tail.

The brain showed extensive hemorrhage into the ventricles and the right internal capsule was almost completely destroyed, the arteries over the base of the brain were moderately sclerotic. The pituitary was normal in shape and consistency, but slightly enlarged (10 by 8 by 6 mm). Serial section was undertaken with the hope of finding a basophilic adenoma. In removing the pituitary it was noted that the dorsum sellae was extremely thin and that the bone was chipped away with ease. In this connection, it should be stated that marked brittleness of bone had also been noted on removing the breast plate.

Histology. The myocardium (left ventricle) shows a moderate hypertrophy. There is considerable albuminous swelling and fragmentation. Kidney the renal capsule is moderately thickened. Most of the glomeruli are fairly well preserved,

many of them are swollen, but very few contain erythrocytes. Some are acutely necrotic with disintegrating capillary tufts. There is a striking tubular necrosis involving mostly the proximal convolutions. The small lobular arteries and arterioles are contracted, and have thickened walls which often are acutely degenerated (acute hyalinization of the media, edematous swelling and subendothelial lamellar fibrosis of the intima). Some small arteries also show an acute arteritis as evidenced by cellular and fibrinous infiltration within the walls, and many are completely blocked by thrombosis. There is very little old interstitial scarring but there is considerable recent edematous and fibroblastic infiltration in areas where the tubular necrosis has been complete and is now undergoing resolution. The picture is that of an acute and subacute cortical degeneration due to arteriolar spasm and stenosis. The larger arteries are moderately thickened or contracted.

The adrenal section shows a prominent hyperplasia of the mid-cortical zone (zona fasciculata). The cells are large, pale staining, and the zone generally widened. In many areas, there appears to be a regenerative process in which nodular collections of cells are seen to be budding out, but no true adenomas are present. Many of these cells showed intense fatty degeneration. The zona glomerulosa is small, the inner (reticulata), moderately enlarged. The medulla is not seen.



FIG 1 Basophilic adenoma, anterior lobe ($\times 27$). At the point of greatest cellular density, there is early invasion of the pituitary capsule.

The pancreas shows acute necrosis of many lobules. The islands share in the destructive process. There is an arteriolitis and marked contraction (spasm?) of the small arteries and secondary thrombosis, similar to that seen in the kidney. There is no true fat necrosis, but apparently ischemic necrosis.

The ovarian section shows a marked sclerosis, the presence of very few small primordial ova, and the absence of any medium sized or maturing follicles. There is one large follicle filled with degenerated granulosa cells. These findings suggest that normal cyclic development and ovarian stimulation were not present in this case. The thyroid and parathyroid were not sectioned. The liver presents a marked congestion and interstitial edema, and fatty degeneration.

In the lower anterior aspect of the pars distalis of the pituitary gland there is a small nodule, 2.5 by 2 mm., that takes the hematoxylin stain and stands out in definite contrast to the lighter stained remainder of the anterior lobe (figure 1). It is definitely circumscribed, separated from the surrounding tissue by rather large encircling sinusoids. The nodule is an adenoma composed of basophilic cells, smaller than the basophilic cells in the adjacent normal tissue, they are in alveolar and cord-like formations, closely aligned. In the central distal portion, the cells are densely packed and deeply stained. The adenoma reaches the pituitary capsule, and at one point, it has infiltrated through it, entering a large sinus in the outermost portion of the capsule (figure 2). The infiltrating cells apparently have been under great



FIG 2 Invasion through the pituitary capsule, into a large sinus. ($\times 115$)

pressure, being greatly compressed at this area. Many of them have practically fused together in their passage into the sinus, so that while the nuclei are more or less intact, the basophilic cytoplasm has some resemblance to a syncytium. Despite the evidence of rapid development of the adenoma, as suggested by the compression exerted on the surrounding glandular tissue, definite nuclear changes of carcinomatous development

are not seen. The invasion through the capsule, however, suggests a malignant tendency. Curiously enough, an occasional acidophile cell is seen in this basophilic adenoma, probably a result of early inclusion.

A small secondary basophilic nodule is seen nearby, consisting of cells of normal basophilic type and throughout the anterior lobe there is an increased basophilism. For a considerable number of serial sections, there is slight but definite invasion of basophilic cells into the pars nervosa (figure 3), and some of them have disintegrated.

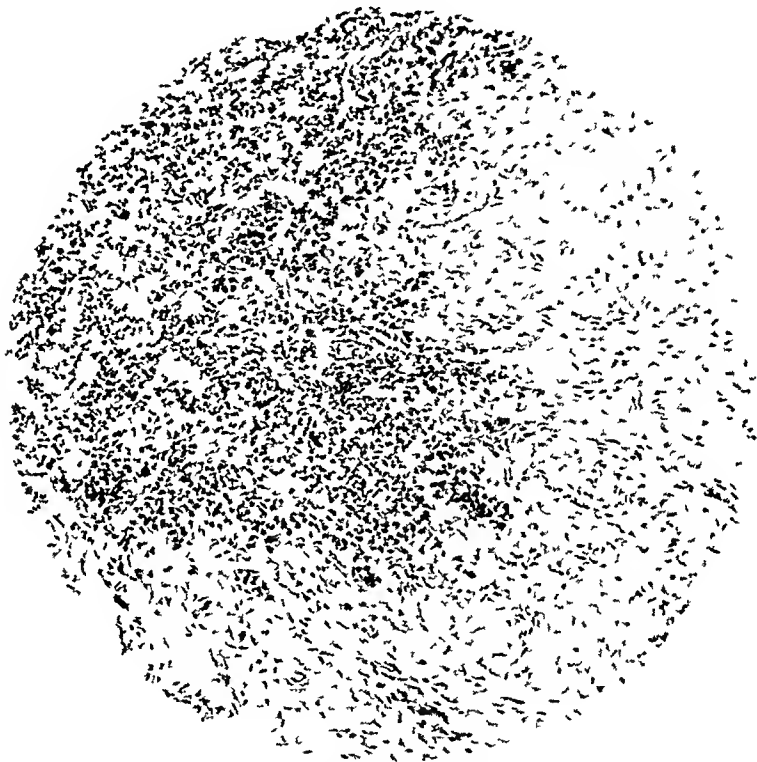


FIG 3 Basophilic invasion of the pars nervosa ($\times 80$)

here (apocrine secretion, indicative of posterior lobe activity, according to Cushing). Section of the stalk shows marked congestion of the hypophysis-portal vessels, but all the pituitary vessels, especially the sinusoids within the anterior lobe, are heavily congested.

DISCUSSION

This patient presented the characteristic physical changes that lately have been linked to basophilic pituitary adenoma. The face was large and broad, and coarse featured, the eyebrows were unusually heavy and bushy and there was a marked hirsuties. The face had apparently not been shaved in the last few days of life and the hair growth was prominent. The large trunk, especially the abdominal enlargement, was in sharp contrast to the narrow forearms, wrists, and feet. Purplish striae were not seen, possibly because they were not looked for.

The clinical aspect of malignant hypertension (the comparatively youthful age level, the rapid course, and the presence of advanced hemorrhagic neuro-retinitis) was corroborated by the presence of severe arteriolar degeneration in the kidneys, accompanied by an acute and subacute degeneration of the parenchyma. The renal changes of malignant hypertension found in cases of basophilic adenoma are discussed in a paper recently published by MacMahon¹¹. Hypertension has been noted in practically every case of basophilic adenoma. This constant association, and the recent investigations of Anselmino in eclampsia make it appear that pituitary activity and hypertension are much more than coincidental. Pituitary basophilism was noted some years ago in association with glomerulo-nephritis, nephrosclerosis and uremia. Unfortunately there was no correlated study of the pituitary gland in the earlier stages of the hypertension that must have preceded those late features of "renal-vascular" disease.

Adrenal hyperplasia has been considered in many quarters to be the primary factor in the pathogenesis of hypertension. Until the work of Cushing, this patient in all probability would have been regarded as suffering from hyperadrenalism or possibly the "diabete hirsute" of the French. There is a well-recognized syndrome of primary hyperadrenalism usually seen as the result of a neoplastic process in the adrenal cortex. It is featured by hypertension and often by virilism. In the light of the recent knowledge of the pituitary adenomas, one wonders what serial section of the pituitary gland would reveal in such cases. Marked secondary changes are now known to occur in the endocrine system as a result of pituitary activity, the adrenals may become hyperplastic, even to the point of development of small cortical adenomas. In this case the mid-cortical zone was definitely hyperplastic (2.5 to 3 mm thick) and heavily infiltrated by lipid substance. Incidentally, the polycythemia seen in some patients with basophilic adenoma, but absent in this case, has been attributed to adrenal stimulation.⁷

The cases of basophilic adenoma previously reported usually presented diabetes mellitus in what might be called a capricious form, often not amenable to insulin and often characterized by waves of exacerbation and regression. The meager history obtained in our case suggested the existence of such a diabetes. The patient had been attending the diabetic clinic in another hospital for almost one year, and was there regarded as having diabetes, she apparently had received no insulin.

The thymus was atrophied, the ovaries were cystic and sclerotic, the thyroid was of normal size and consistency. In this state of pituitary basophilism the thyroid is usually inactive and often small. Sections for histologic study were either lost or not cut, also in the press of time and in the concentration of our attention on the pituitary gland, the removal of the parathyroid glandules was neglected, there was nothing in the gross appearance that suggested growth or undue hyperplasia. In previous case reports, with one possible exception,⁸ no primary neoplasm of the para-

thyroids was found, although decalcification was occasionally the outstanding clinico-pathological feature. As already stated, abnormal decalcification was noted in this patient, the dorsum sellae was chipped away as if it were made of the thinnest paper-like shell. Decalcification in this structure was noted both in the roentgenologic and in the necropsy examinations in the cases of Parkes-Weber⁹ and Turney¹⁰.

The pituitary gland was slightly enlarged, but of normal shape, in fact, the gross appearance of the gland was disappointingly normal, and this re-emphasizes the need for serial section in a case that clinically suggests the presence of basophilic pituitarism. It explains the failure of distinguished continental pathologists to discover the basis of the peculiar syndrome after they had examined the pituitary, it also accounts for the negative pituitary findings of brain surgeons in operations on patients who probably did have basophilic hypophyseal adenoma. One marvels that such a small lesion could be of such importance. It was found by Parkes-Weber⁹ in a typical example of the now recognized associated syndrome, but at that time he refused to believe that it could possibly give rise to such remarkable systemic effects. In the series of 14 proved cases tabulated by Cushing, only two or three achieved such macroscopic enlargement as to be able to cause the local pressure changes usually attributable to pituitary neoplasms and cysts.

In this patient, the pituitary gland showed of course, as its main structural change, the basophilic adenoma, but two other features deserve special comment.

Histologic examination showed a slight, but definite, basophilic invasion, from the anterior lobe into the pars nervosa. While this was slight, in contrast to the considerable invasion reported by Cushing, it was extant for a considerable distance along the border of the pars nervosa, being noted in a fairly large number of serial sections. Cushing believes that basophilic invasion activates the pars nervosa so that the pressor function of that lobe is accentuated. More specifically he believes that the basophilic cells disintegrate on invasion into the pars nervosa, in the process of an apocrine secretion, that the products thus formed, eventually find their way into the hypothalamus, the infundibular canal and the third ventricle, and that excessive infiltration of this type is the pathological basis of the hypertensive states such as eclampsia and essential hypertension¹². This attractive theory of course must stand the acid test of time, if it does so and becomes an established fact, the study of the development of pituitary basophilism and the manner of access of the basophilic products to the systemic circulation, will obviously be of the utmost importance.

The second histologic feature in this case may, therefore, be of more than casual interest, this adenoma although structurally not carcinomatous had forced its way into a large vascular space which evidently was a sinus (a branch of a cerebral venous sinus) within the pituitary capsule. It was a matter of discussion as to whether this channel was a real blood sinus or an

unusually large lymphatic space. It was lined by delicate vascular endothelium and contained some blood cells, at any rate, there was indication of rapid anatomical invasion and the injection into the systemic circulation of possibly large amounts of the secretion of a hyperplastic ductless gland.

SUMMARY

On the basis of certain physical characteristics, and structural changes, in a woman aged 37, a tentative necropsy diagnosis of basophilic hypophyseal adenoma was made and verified by serial histologic section. The clinical history indicated the presence of diabetes mellitus and the malignant form of hypertensive disease. In this connection, there was interesting histologic evidence of severe and relatively acute arteriolar disease in the kidneys and to a lesser degree in the pancreas. The pituitary adenoma, although small, had invaded a large sinus within the pituitary capsule.

The writer is indebted to Dr. Harvey Cushing, Dr. Louise Eisenhardt, and Dr. H. E. MacMahon for their examination of the microscopic sections, and to Dr. Edwin Heller for the privilege of reporting this case.

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ARTIFICIAL PNEUMOTHORAX THERAPY ⁴

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THE most extensively used and the most successful procedure of compression therapy in the treatment of pulmonary tuberculosis is artificial pneumothorax. Other procedures of compression or collapse therapy should be used when pneumothorax is impossible, unsuccessful, or when indicated as an adjunct to the compression and relaxation obtained by pneumothorax induction.

When the tuberculous involvement is apparently limited to one lung and is of a character considered of sufficient clinical significance, unilateral pneumothorax is indicated. When this character of involvement exists in both lungs, bilateral pneumothorax is indicated.

In treating a large group of cases by this type of therapy, certain difficulties will be encountered which may preclude the induction of pneumothorax or at best the pneumothorax will be unsatisfactory. Through success, partial success or failure, the series of cases selected for this particular type of compression therapy will be automatically subdivided in the following case groups:

- 1 Unilateral pneumothorax with hemidiaphragmatic paralysis
- 2 Pneumothorax with contralateral hemidiaphragmatic paralysis
- 3 Bilateral pneumothorax
- 4 Thoracoplasty with contralateral pneumothorax

The size of these case groups should be as in the order named. All therapeutic pneumothoraces should be instituted very gradually, increasing the degree of compression until the desired amount is obtained. When the necessary compression is obtained, it should be maintained by frequent small refills, sufficient to maintain the desired area in a relatively static compression state and yet allow relatively uninvolved portions partially to reexpand. Carefully induced and carefully maintained collapse produces an expansile type of pneumothorax which not only greatly lessens the development of complication but aids in accomplishing reexpansion of the treated lung at the termination of the therapy. Each case should be conducted individually, carefully judging lung compression and need of compression by frequent fluoroscopy. No case should receive a pneumothorax refill without fluoroscopic observation immediately preceding the refill. It is believed that fluoroscopy after each refill is a worthwhile observation.

To conduct pneumothoraces properly, the attending physician must constantly consider the individual's precompression pulmonary disease with special consideration of the initial amount and type of disease when pul-

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monary reexpansion is contemplated This consideration must of necessity involve a detailed study of parenchymal infiltration and pulmonary cavities as to extent, character and location

Consideration of these factors is of great aid in determining the duration of the therapy Pneumothorax therapy is terminated when there is definite disease arrest over a satisfactory period Disease arrest is determined by an accurate estimate of the patient's clinical status and this estimate is made from a composite picture of all clinical data available In this estimation, great importance is attached to roentgen-ray interpretation and since the problem of determining an accurate clinical status is a problem of the clinician, he should be the one who makes the interpretation of the roentgen-ray film Serial roentgen-ray films are our greatest aid in observing pulmonary changes incident to compression therapy

The opinions just enumerated are well known to all phthisiologists The value of artificial pneumothorax therapy is so well established that the procedure is seldom discussed in the current medical literature Discussion of the subject, however, is warranted because suitable cases for pneumothorax treatment exist in all sanatoria, yet are under a regime of ordinary rest treatment The procedure is not employed nearly so extensively as it should be, as too many suitable cases are on rest regime and will remain so until disease progression or some emergency demands the induction of pneumothorax During periods of unwarranted delay, these patients are subjected to the potential dangers of hemorrhage and bronchogenic spread of the disease Since, in most instances, pleural involvement is a part of the tuberculous process, a continuation of pleural apposition will often result in new formed pleuro-pulmonary adhesions or even in pleural symphysis In many instances, a delay ends not only in disease progression but by pleural changes, and through these latter the patient is denied the advantage of the most powerful weapon to combat the progression of pulmonary tuberculosis

The success of unilateral artificial pneumothorax therapy is well established and a discussion of results obtained would serve no particular purpose We believe, however, that in many instances this most useful therapy is either much delayed or even denied the patient through fear of attendant complications It is my belief, however, that the unfavorable potentialities of an active pulmonary tuberculous process are to be feared far more than those of an induced pneumothorax

We have studied and accurately tabulated the various complications in 700 pneumothoraces induced and conducted on one of the tuberculosis units at Fitzsimons Hospital Presentation of these data may tend to help allay apprehension in regard to the use of this valuable procedure of compression therapy

Hydropneumothorax of clinical significance occurred in 34.5 per cent of cases, pyopneumothorax in 5.8 per cent, superimposed spontaneous pneumothorax in 13.7 per cent, air embolism in 0.57 per cent Mortality from complications has, in the main, resulted directly or indirectly from superimposed

spontaneous pneumothorax, directly because of a large patent pleuro-pulmonary fistula, indirectly because of subsequent development of pyopneumothorax. There were no deaths from air embolism in this series of 700 cases.

Unilateral Pneumothorax with Hemidiaphragmatic Paralysis We have found pleuro-pulmonary adhesions to be an etiologic factor in the development of complications in pneumothorax therapy. We have concluded that hemidiaphragmatic paralysis decreases the tension upon pleural adhesions which lessens the probability of certain complications. It was noted in the beginning, when the various classes of pneumothoraces were enumerated, that unilateral pneumothorax included the adjunct of hemidiaphragmatic paralysis. This was done for the following reasons:

- 1 Hemidiaphragmatic paralysis is of value as a supplement to artificial pneumothorax therapy when additional compression and relaxation are required for cavity obliteration because of pleuro-pulmonary adhesions.

- 2 Artificial pneumothorax complicated by acute pleuritis with or without serous exudation may tend toward obliteration of the pneumothorax space. Untimely oblitative pneumothorax may end in disease progression unless some procedure of compression therapy is substituted for the pneumothorax. We advocate that this procedure be hemidiaphragmatic paralysis.

- 3 Upon completion of a successful pneumothorax, paralysis of the hemidiaphragm is indicated as a preexpansion procedure. Diaphragmatic elevation decreases the size of the hemithorax and this diminishes the degree of pulmonary reexpansion required, decreases or prevents mediastinal retraction and causes permanent continuation of some compression and relaxation. There is also the safety factor of some decrease in pulmonary function.

- 4 It is indicated as an adjunct when the pneumothorax is unsatisfactory because of partial pleural symphysis.

- 5 When artificial pneumothorax, after a sufficient period, fails to obliterate midlung cavities, hemidiaphragmatic paralysis is indicated.

We have concluded that paralysis of the hemidiaphragm is of value when certain factors tend to make the artificial pneumothorax unsatisfactory and when, though the pneumothorax therapy has been successful, pulmonary reexpansion is contemplated. Since it is of value under unfavorable conditions and since it is advocated as a preexpansion procedure, we see no reason why practically all cases of artificial pneumothorax should not have the advantage of hemidiaphragmatic paralysis.

ARTIFICIAL PNEUMOTHORAX WITH CONTRALATERAL HEMIDIAPHRAGMATIC PARALYSIS

In bilateral active pulmonary tuberculosis, contralateral phrenic exeresis is indicated under the following conditions:

- 1 When pneumothorax is impossible on one side.
- 2 When pneumothorax does not produce the desired pulmonary compression.

3 As the procedure of choice when the character and distribution of lesions are such as to promise favorable results by hemidiaphragmatic paralysis

In moderate or far advanced pulmonary tuberculosis, one of the chief difficulties of utilizing bilateral compression by induced pneumothorax is that of extensive pleuro-pulmonary adhesions or pleural symphysis, complete or partial. Attempts to induce pneumothorax fail or at best yield unsatisfactory results. Paralysis of the hemidiaphragm is then induced as a suitable procedure of pulmonary compression. This measure may be instituted with a view of obtaining the desired result or used merely in an attempt to control disease progression during the interval of bringing under control the tuberculous lesions of the opposite side. If the latter problem is the situation, it may be necessary later to perform thoracoplasty upon the hemithorax presenting pleural symphysis.

In other patients in whom a successful pneumothorax has been induced upon the more involved side, the type and distribution of the lesions of the contralateral lung may be such as to be controlled by hemidiaphragmatic paralysis. In other words, it is estimated that it will be unnecessary to induce a bilateral pneumothorax and, instead, the less radical procedure of phrenic exeresis is at least given a trial for a satisfactory period. In the event that the desired results are not obtained, some other more drastic procedure may then be attempted.

Phrenic exeresis with its subsequent diaphragmatic paralysis, elevation and immobilization, often yields excellent results when applied to properly selected cases. In other instances, though disease arrest is not accomplished, the desired aim of the procedure is obtained. The success of any compression procedure is established if it really accomplishes the clinician's intended aim. Phrenic exeresis has doubtless suffered somewhat as to its reputation as a curative compression procedure because of instances of its wholesale application in the treatment of pulmonary tuberculosis. Any method of therapy meets with success only when applied with reasonable discrimination.

Paralysis of the hemidiaphragm in properly selected cases often produces excellent results even when used as the sole measure of pulmonary compression. This measure is capable of preventing disease progression in one lung during the interval of pneumothorax therapy on the opposite side. This course of action may be essential prior to the induction of radical chest surgery.

BILATERAL PNEUMOTHORAX

In treating any large series of cases of pulmonary tuberculosis, one encounters many patients in whom the application of unilateral compression therapy procedures is precluded because of extensive bilateral disease. In this group, bilateral pneumothorax should be attempted and when difficulties hinder or prevent its successful employment, other measures of compression or collapse therapy should be instituted.

In discussing unilateral pneumothorax, most phthisiologists advocate its use on the basis of their inability to obtain and maintain disease arrest by the so-called "rest cure" If they doubt their ability to treat tuberculosis satisfactorily when the disease process is relatively confined to one lung, how can one expect to accomplish results by this method when the disease process is definitely bilateral? If unilateral pneumothorax is indicated in relatively unilateral tuberculosis, it is believed that bilateral pneumothorax is urgently needed when an active disease process involves both lungs

Frequently patients are advised that they are unsuitable subjects for artificial pneumothorax therapy because the contralateral lung presents active involvement entirely too extensive to withstand compression of the more involved side The patient is advised to undergo routine rest treatment with a view of improving the better side sufficiently to warrant the induction of unilateral pneumothorax In instances, this procedure may yield satisfactory results but in the majority of instances, the interval of delay allows disease progression sufficient to preclude the induction of unilateral compression Delay subjects the patient to all the potential dangers of active tuberculosis or of cavitation which are so often stressed in unilateral tuberculosis and which are even more imminent in bilateral disease

Results from bilateral pneumothorax are not as excellent as those usually obtained from the unilateral procedure We must bear in mind, however, that we are dealing with patients presenting far advanced tuberculosis in whom the tuberculo-immune qualities may be depressed These patients are generally those who have suffered a more or less severe bronchogenic spread from the older involved lung to the contralateral lung Often it is this recent disease extension that brings the case initially to the sanatorium In other instances the extension occurs in cases of long standing that have been trying to "carry on" in spite of chronic pulmonary tuberculosis Due to the fact that the disease process is frequently of long standing in one lung, it is difficult because of pleuro-pulmonary adhesions or pleural symphysis to induce a satisfactory pneumothorax Complications encountered in conducting bilateral pneumothorax are frequent and often severe but in considering this fact we must again consider that we are dealing with cases of far advanced tuberculosis with, in most instances, a hopeless prognosis if untreated In considering the possibility of complications, one should remember that in far advanced tuberculosis untreated by compression therapy, certain extra-pulmonary tuberculous complications such as laryngitis or enterocolitis may soon make their appearance, possessing a gravity far outweighing the usual complications of bilateral pneumothorax Extensive bilateral disease demands immediate compression treatment and the application of this therapy should be carried out with great care

We have induced and carried on bilateral pneumothorax in 93 cases of bilateral pulmonary tuberculosis Many of these cases have not been completed and end results cannot be reported May it suffice to state that results have been very gratifying and we enthusiastically advocate the procedure

In 1931, after a careful analysis of 25 cases treated by bilateral pneumothorax, we recorded the following conclusions

- 1 Advanced bilateral pulmonary tuberculosis may be arrested by bilateral pneumothorax

- 2 Bilateral cavitation may be eradicated

- 3 A rapid fatal termination from bronchogenic spread to the contralateral lung may be prevented by converting the case from a unilateral to a bilateral pneumothorax

- 4 Bilateral pneumothorax, even when unsatisfactory on one or the other side, may cause sufficient improvement to warrant the utilization of surgical collapse previously precluded because of extensive bilateral disease

After three more years of experience with bilateral pneumothorax we do not wish substantially to alter these conclusions

THORACOPLASTY IN THE PRESENCE OF CONTRALATERAL PNEUMOTHORAX

In cases of bilateral pulmonary tuberculosis, the induction of artificial pneumothorax may be impossible or at best unsatisfactory on the more massively involved side because of complete pleural symphysis or a pleural symphysis over the involved area. The lesser involved side may present sufficient involvement to preclude radical surgical collapse contralaterally. This group has been successfully treated by first inducing pneumothorax for compression of the better lung and when compression is well established and maintained by weekly refills, a thoracoplasty is performed on the massively involved side. In the event that it seems advisable to delay the institution of surgical collapse, a hemidiaphragmatic paralysis is performed to maintain in a quiescent state or to improve the tuberculous process during the interval of delay. Phrenic exeresis is not routinely performed in these cases since in some instances it may be advisable to conserve pulmonary function.

We have performed thoracoplasty in the presence of contralateral pneumothorax in 11 cases and have instituted contralateral pneumothorax in another case shortly after thoracoplasty. Excellent results have been obtained in this small series of cases as 11 cases are living in a group of 12 cases where the prognosis, without bilateral compression therapy, seemed hopeless. One case died several months after thoracoplasty, of disease other than tuberculosis.

It is interesting to note that all of these cases endured major chest surgery extremely well. When thoracoplasty is performed in the presence of contralateral pneumothorax, we have done so in the presence of a reduced contralateral pulmonary compression and this compression has been maintained in a reduced status during the postoperative convalescence. In these cases, it is essential that the extent of rib resection be cautiously estimated, limiting the operation according to the patient's ability to withstand the operative procedure. Four of our cases had their thoracoplasty performed in two stages and eight cases were operated on in one stage.

In cases requiring bilateral compression therapy where it becomes necs-

sary to perform thoracoplasty, it seems of extreme importance thoroughly to collapse the involved area and to leave as much functioning pulmonary tissue as possible. This is accomplished by subtotal costotectomy over the involved area. In bilateral pulmonary tuberculosis where pneumothorax cannot be induced with success on the more involved side, thoracoplasty may be performed with success when the disease of the contralateral lung is under control by artificial pneumothorax.

In conclusion, we believe that the evolution of artificial pneumothorax therapy has resulted in its greatly increased applicability. Groups of cases, as enumerated above in which pneumothorax has been successfully employed, clearly demonstrate the scope of its present day usefulness. A decade ago, certain indications for the use of pneumothorax, now confirmed by successful application, would have seemed radical, probably too radical. For instance, the use of pneumothorax contralaterally in the presence of thoracoplasty might have been condemned by some of the prominent phthisiologists. The progress in pneumothorax therapy has been of a very creditable character and the workers who have contributed to this progress have added much to the control and treatment of pulmonary tuberculosis.

CLOSED INTRAPLEURAL PNEUMOLYSIS

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THE marked progress which is steadily being made in the surgical treatment of pulmonary tuberculosis demands that we frequently report the progress achieved by any particular procedure of compression therapy. Such a report must include not only a description of any improvement in operative technic but also recommendations regarding the selection of cases with an accurate survey of the results obtained by the particular method. The particular procedure to be discussed in this paper is closed intrapleural pneumolysis utilizing the electro-surgical method. The report is based upon my experience in 30 thorascopies with the cauterization of adhesions in most instances. The cases herein described, however, include only the 17 operated upon by the electrosurgical method between the periods July 1, 1931, and March 1934. They illustrate the results which may be obtained when properly selected cases are placed under the care of one competent and properly equipped to perform the Jacobaeus operation.

Intrapleural pneumolysis is an operative procedure for severing adhesions, extending between the parietal and visceral pleurae, which prevent satisfactory collapse of the affected lung. The closed method, as originally presented by Jacobaeus in 1913 and later modified by Unverricht and Matson, is the operation of choice. We have found the incidence of this operative requirement during the past five years to be approximately 5 per cent of all our artificially induced pneumothoraces. More recently this percentage has been decreased due largely to our adoption of phrenic exeresis as an integral part of pneumothorax therapy. However, in some cases phrenic avulsion may be contraindicated, and when adhesions prevent collapse a lung cavity may remain patent in which instance the Jacobaeus operation becomes mandatory. An appreciation of results obtained may be gathered from Moore's recent exhaustive survey of the literature in which he collected 1850 cases reported by 45 different authors.¹ Of these, 75.5 per cent were clinically successful. The operative mortality was 1.08 per cent and 4.5 per cent were made worse by the operation. When compared with 52 collected cases of open pneumolysis, these results are far superior to the latter operative method. In the open type of operation, the operative mortality was 19.2 per cent with a like percentage of cases made worse by operation and only 57.6 per cent were clinically successful. Consideration of these figures makes further comparison unnecessary especially under present operative methods.

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From the Medical Service, Fitzsimons General Hospital, Denver, Colo.

INDICATIONS

The operative indications include those for thoracoscopy and those for cauterization at the thorascopic examination. The difference is fundamental in that the indications for cauterization are entirely dependent upon the thorascopic findings. Results will, to a very appreciable degree, depend upon the experience and judgment exercised in the selection of adhesions for cauterization at thoracoscopy. Broadly speaking, we believe that regardless of location, thoracoscopy is indicated in all cases under pneumothorax therapy with unsatisfactory pulmonary compression over the diseased areas because of pleural adhesions, when the unsatisfactory compression is not obviously due to adherent lung tissue. Whether or not an attempt is made to cut offending adhesions is determined by intrathoracic inspection.

CONTRAINDICATIONS

We have recognized no contraindications to thoracoscopy if the indications just enumerated are present. The presence of a bilateral pneumothorax only makes it more urgent. The presence of a virulent pyopneumothorax would contraindicate cauterization and therefore thoracoscopy would be unnecessary, however, a chronic purulent exudate, in an afebrile patient, is not a contraindication. The tuberculous disease may be so extensive that little hope for recovery exists even though the adhesions be severed, and in such cases thoracoscopy is not warranted. Since thoracoscopy is essentially free from danger, each case must be adjudged on its own merits and the patient given the benefit of the procedure, provided that the operator does not attempt such impossible tasks that his inevitable poor results bring the procedure into disfavor. Unwise selection of cases for cauterization should result in criticism of the operator rather than in condemnation of the surgical procedure.

SELECTION OF CASES

The operator should be competent to select the cases for operation. He should be trained in phthisiology, experienced in pneumothorax therapy and a competent surgeon. At present, few possess such qualifications, and cases are selected by the cooperation of the phthisiologist, roentgenologist and surgeon. Careful evaluation of the clinical course of the disease together with meticulous study of serial roentgenograms before and during the course of pneumothorax therapy is essential. A word of caution is necessary, operability cannot be determined on roentgenographic study alone as it is impossible from a study of the films to determine accurately the number, width, or thickness of adhesions, one cannot determine whether only the edge or entire width of the adhesion is shown. At times it is questionable whether we are dealing with adhesions or adherent lung, or to what extent both are present. The adhesions are more numerous and generally larger than they appear on the film. Thus, roentgenographic study is of value in

selecting cases for thoracoscopy and as an aid in determining the site for introduction of the thoracoscope but decision regarding cauterization can be made only by inspection of the adhesions through the thoracoscope

TECHNIC

The technic which we have found most valuable and have used during the past three years is the electrosurgical method as presented by Matson.² The advantages of this method are First, with more adequate coagulation it is possible to prevent or control hemorrhage. Second, less heat and smoke are produced decreasing the extent of tissue reaction at the site of cauterization. Third, postoperative complications are decreased. Fourth, manipulation of the electrode within the thorax is less difficult than is the handling of the rigid cautery.

PARTIAL CAUTERIZATION OF ADHESIONS

It has generally been understood that the offending adhesions are completely severed at operation, while this is desirable, it is often impossible and at times unnecessary. Our experience has shown that the partial or incomplete cauterization of the larger adhesions is often followed by the closure of the cavity under continued pneumothorax therapy. Repeated operations may be necessary, however, a satisfactory pneumothorax may result from a single partial cauterization. String, cord-like or fan-shaped adhesions, and small bands often interfere with the pulmonary compression but fortunately offer few operative difficulties. Funnel-shaped or diffuse fold adhesions, and large bands greatly increase the operative difficulties. This is due to three factors. First, the fibrous tissue of the adhesions and the lung itself may be indistinctly blended, making differentiations between the two structures almost impossible. Second, the parenchymal tissue may extend into the adhesion and contain the prolongation of a cavity, and large blood vessels may be unrecognizably imbedded within the adhesion. Third, these larger adhesions, especially those situated apically, may be of such a structure and location that it is impossible to view their entire circumference during the thoracoscopic survey. Such difficulties demand strict individualization of cases, accurate orientation and interpretation of the thoracoscopic findings. It is necessary, at this stage in the operation, for the surgeon to determine what procedure he will follow, whether complete cauterization, partial cauterization, coagulation of the parietal pleura attachment alone, or whether he will recommend some other operative procedure. The following facts are important in arriving at this decision. First, the patient may have declined the recommendations for other collapse therapy, especially thoracoplasty, or the patient's general clinical condition may have precluded this operative measure. Second, experience has taught us that, in general, certain more or less arbitrary rules are applicable in operating upon these difficult adhesions. If the adhesion is situated laterally and is of a large band or shelf structure with one or more inches between the parietal pleura and lung,

cauterization is indicated. Partial cauterization is preferable if the structure is dense and considerable time would be required for complete severance, in which instances, from one-fourth to one-half of the parietal pleura attachment can be cauterized with safety. If the adhesion is apical and presents an inch or more of free surface, partial cauterization is again the procedure of choice. If there is less than one inch of free adhesion surface, cauterization is contraindicated. Two courses are then available: first, the surrounding parietal pleura attachment may be coagulated and a higher positive pressure pneumothorax utilized to stretch the adhesion so as to permit cauterization later, or second, thoracoplasty is recommended. Thus, it is evident that with larger and more difficult adhesions, thoracoscopic examination must make the differential determination between the operative procedures of intrapleural pneumolysis and thoracoplastic surgery.

COMPLICATIONS

The complications incident to this operation may be divided into the immediate and the postoperative. The immediate include those which occur at the operation, such as hemorrhage and pulmonary damage. Of the 1850 collected cases, hemorrhage occurred in 1.5 per cent and was fatal in only one instance. Thus, this complication cannot be considered frequent or serious. Damage to the lung parenchyma results from technical errors and is generally due to the cauterizing of lung tissue contained in the adhesion. The partial severance of large adhesions may be followed by an immediate or delayed superimposed spontaneous pneumothorax because of a spontaneous rupture of the unsevered portion of the adhesion.

The second group of complications is postoperative and includes subcutaneous emphysema which is rarely of clinical significance. Pleural effusion occurs in practically all cases but is generally rapidly absorbed while fluid present before operation often disappears following the cutting of adhesions. The effusion may at times develop into a tuberculous empyema especially if the surfaces of the pleurae are studded with tubercles which become activated by intrapleural instrumentation. Mixed infection empyema develops by the complication of a superimposed spontaneous pneumothorax and its concurrent pleuro-pulmonary fistula. This occurs in two ways: first, as the result of the rupture of a partially severed adhesion at its pulmonary attachment and, second, as a delayed complication resulting from sloughing of the devitalized pulmonary end of the adhesion. The general clinical condition of the patient, the status of the contralateral lung, the size and type of lung perforation and treatment instituted largely determine the end result in these cases.

Our experience has been that the tissue necrosis at the site of the cauterized lung attachment or the tearing of partially severed adhesions is the most frequent cause of superimposed spontaneous pneumothorax followed by development of a pyogenic empyema. Activation of tubercles within the cauterized adhesions, the breaking down of subpleural caseating

areas, or the sloughing of the cauterized tissue is often the cause of this complication and unfortunately is unavoidable

It has been our bitter experience to witness all the usual complications and in two instances unusual complications, in one, an extensive aspiration tuberculous pneumonia in the contralateral lung, and in another, severe post-operative hiccoughs. However, the complications usually attributed to this operation do, as is well known, occasionally develop in cases in need of but not subjected to the operation. Pleural effusion is more frequent in this group of pneumothorax cases while tuberculous empyema may develop, and superimposed spontaneous pneumothorax is likewise more apt to occur in pneumothorax cases having pleural adhesions holding cavities patent. In the 1850 collected cases operated upon, serous effusion developed in 30 per cent, tuberculous empyema in 2.2 per cent and pyogenic empyema in 1.8 per cent¹. These figures compare favorably with those of any large group of pneumothoraces. In this small series of 17 cases operated upon by the improved electrosurgical method, three or 18 per cent developed fluid after operation, and in a like percentage fluid present before operation decreased or disappeared afterward. Tuberculous empyema developed in one case (6 per cent) and pyogenic empyema in one case. In both of these cases, the patients were less than 21 years of age, very toxic and had extensive bilateral disease with cavitation. Superimposed spontaneous pneumothorax occurred in two (12 per cent) of the cases. In one instance a purulent exudate developed and in the other only a small collection of serous fluid appeared three months later. An obliterative pleuritis occurred in one case with the subsequent loss of the pneumothorax space. Hemorrhage did not occur in this series. The worst complication is the development of a purulent exudate and although it markedly reverses the prognosis, it generally yields to correct therapy. We believe the correct therapy, at present, to be disinfection oleothorax using gomenolized oil for tuberculous empyema, and aqueous gentian violet solution for mixed infection empyema. Energetic treatment by frequent aspiration of the purulent exudate followed by irrigation and instillation of the solution indicated into the pneumothorax space yields satisfactory results, thoracoplastic surgery being used at a later date if necessary to obliterate the space. Only one of this group has required thoracoplasty.

RESULTS

The results achieved by this operation can be adjudged only upon whether or not a satisfactory pneumothorax is produced. The late results, namely, cavity closure, are more correctly the achievements of pneumothorax therapy and although that is the end desired in all cases it alone cannot be considered as an accomplishment or a failure of the Jacobaeus operation. In this series 82 per cent of the patients had a satisfactory pneumothorax following operation. In eight cases the pneumothorax was considered excellent. In five cases the adhesions were only partially severed or others

remained which prevented the production of a complete collapse, however, satisfactory compression of the diseased area was obtained. In the follow-up study, 76 per cent had closed their cavities within or less than one year. Two of the patients died in less than six months from progression of the disease, in one, operation hastened death, but in the other life was prolonged. In one case the cavity remained patent after one year and thoracoplasty was done. A satisfactory pneumothorax was present in another patient who left our care five months after operation and his condition is unknown.

In conclusion, we wish to draw attention to this valuable adjunct in the treatment of unsatisfactory pneumothoraces due to pleural adhesions. At the same time it is desired to caution against its indiscriminate use and urge that the proper equipment be available and that experienced operators perform the operation. It is doubtless the most difficult operative procedure now utilized in the compression therapy treatment of pulmonary tuberculosis. Its complications may be serious but its many gratifying results generously repay for the diligence required in its proper execution.

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THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM", A REVIEW OF RECENT AMERICAN AND ENGLISH LITERATURE ON "RHEUMATISM" AND ARTHRITIS*

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IN THREE PARTS

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Rheumatism, using the term in its broadest sense, has just been designated "Public Enemy Number Ten" by the United States Department of Public Health. Over the world similar departments are placing this disease-group high on the list of those which present a major challenge to the medical profession and public. Chronic arthritis, the most common form of "rheumatism," is the greatest single cause of disability in temperate climates, and it produces more pensionable invalidism than any other condition except cardiovascular disease in old age. In spite of the fact that chronic arthritis is the oldest recorded disease, the medical profession has to a considerable degree ignored it. Because of this indifference, there has long existed an attitude of pessimism concerning it.

In 1924, the continuation of such a state of affairs was challenged by the formation of the "Ligue Internationale Contre le Rheumatisme." Since

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then many national committees have been created to act in affiliation with this league, the American Committee for the Control of Rheumatism being established in 1928 (Pemberton¹) Much investigative work has been carried on, societies have arranged and journals have published symposia on various phases of the "rheumatic diseases" The profession has at last become exceedingly articulate in regard to the subject

Interest has become so widespread, and clinical contributions and experimental investigations of merit have become so numerous, that a number of special journals have been created in other countries to present these developments^{2,3} The transactions of several conferences and congresses have been published separately,⁴ and yearly reviews of literature on these topics are now published from several countries, especially from France and Germany^{5,6,7,8} In spite of the fact that workers in the United States, Canada, and Great Britain have been as active as, and indeed in some phases more active than those in other countries segregation of their publications in a special journal has not seemed wise No systematic review of the work published in English has appeared, nor has it been comprehensively presented in foreign surveys Therefore, at the request of the American Committee for the Control of Rheumatism, the authors have attempted to prepare a correlated synopsis of the recent significant literature of these countries It is planned to present subsequent reviews, perhaps annually, including such editorial comment as may seem helpful In this first review certain "background" notes are included, and critical annotations are brief

RHEUMATISM AS A PUBLIC HEALTH PROBLEM

General Incidence and Economic Considerations Disease becomes a social problem when the person afflicted is either a danger or a burden to his fellow citizens Disease becomes an industrial problem when it leads to disorganization of industry by causing frequent or prolonged absence of employees from their work Thus defined, rheumatism is a social and an industrial problem of the greatest magnitude (Fox⁹) Chronic rheumatism is not the cause of much mortality, aside from the consequences of rheumatic fever However, on account of its morbidity rather than its mortality it is productive of an enormous economic loss, the degree of which has until recently not been fully appreciated

Statistics on the incidence of rheumatic disease have been meager Stimulated perhaps by the investigations of the British Ministry of Health (Glover and Newman,¹⁰ 1924) fragmentary statistics are now being made available from various quarters, but statistics in this country do not approach the comprehensiveness of those of the British Since the report of the Ministry of Health is basic and quoted widely (Connan,¹¹ Fox,¹² Boyd,¹³ Buckley,¹⁴ Copeman¹⁵⁻¹⁶), its figures bear repetition here Records concerned the illnesses for one year of 91,000 insured persons (58,000 males, 33,000 females) During the year about 28 per cent (27.6 per 1,000)

of these insured persons consulted their physicians for rheumatism (total 2,510, males 1,771, females 739) Thus about 30 of each 1,000 insured men and 22 of each 1,000 insured women suffered from some kind of rheumatism during the year

On the basis of these figures it was estimated that in England, with an insured population of 16,000,000 persons, more than 400,000 of them in any given year were suffering from one of the rheumatic diseases How formidable is the morbidity from chronic rheumatism will be seen from the estimate that it produces one-sixth of total industrial invalidism In 1922, rheumatism in England was responsible for a loss to workers of more than three million weeks of work and for the payment in sick benefits of about two million pounds In 1927, sick benefits for rheumatism were about five million pounds Adding to this the estimated loss in wages for the five and a half million weeks of work lost, the cost of rheumatic diseases to the country in that year was approximately between seventeen and twenty million pounds—\$85,000,000 to \$100,000,000 (Kinnear, 1928, Buckley¹⁷)

Dublin,¹⁸ analyzing surveys by the United States Public Health Service and by the Metropolitan Life Insurance Company, has given us the only comprehensive American statistics on mortality and morbidity In the United States about 10,000 deaths are charged annually to rheumatism of all forms, 4,000 deaths being directly, and 6,000 deaths indirectly, due to acute or chronic rheumatism Of the deaths directly due to rheumatism, two-thirds are caused by rheumatic fever, one-third by "chronic rheumatism, arthritis, and gout" In recent years the death rate from rheumatism has been about 4 per 100,000 persons (between 2 and 3 per 100,000 for rheumatic fever and a little more than 1 per 100,000 for chronic rheumatism) Thus rheumatism causes an insignificant proportion of the annual death, only 0.4 per cent of all deaths

When we turn to sickness and disability due to rheumatism, however, the picture is altogether different The survey of the United States Public Health Service concerned Hagerstown, Maryland, that of the Metropolitan Life Insurance Company many large, widely scattered cities and towns In all the communities surveyed, rheumatism was one of the outstanding causes of disability The first study differs from the second in that it included all illnesses occurring over a period of time, whereas the latter was a report of sickness prevailing at a given time The Metropolitan's figures concerning 600,000 persons showed that 164.4 persons per 100,000 were reported as suffering from rheumatism This disease-group accounted for nearly 9 per cent of all cases of illness As a cause of disability rheumatism was outranked only by accidents, which caused but 5 per cent more disablement, tuberculosis accounted for less than half as much, organic heart disease and cerebral hemorrhage only two-fifths and cancer less than a tenth as much The Hagerstown survey indicated an annual rate of sickness caused by articular rheumatism and gout of 16.6 per 1,000, and in addition such illness as muscular rheumatism, lumbago, and associated conditions numbered 3.0

per 1,000 Here again rheumatism caused more illnesses than any other disease of long duration, its disability rate was therefore 16.6 per 1,000 (19.6 if one adds muscular rheumatism), that of heart disease 10.1, arteriosclerosis 1.2, cerebral hemorrhage 0.7, paralysis 1.5, cancer 1.3, and diabetes 0.9 (Dublin¹⁸)

A recent survey of chronic diseases in Massachusetts (Osgood,¹⁹ Bigelow and Lombard²⁰) indicated that nearly 12 per cent of the total population was suffering from some form of chronic disease. It is estimated that in Massachusetts alone about 140,000 people are suffering from chronic rheumatism (3.2 per cent of its population of 4,380,000), and that there are more cases of chronic rheumatism than of heart disease, tuberculosis, and cancer combined. There were 11,500 cases of cancer, 16,000 of active tuberculosis, 84,000 of heart disease, and 138,000 of rheumatism. In Massachusetts there are therefore over half again as many cases of "rheumatism and arthritis" as of heart disease, approximately eight times as many cases of rheumatism as of tuberculosis, and 12 times as many cases of rheumatism as of cancer. (For other recent studies on incidence see "Publication No. 2," Committee on Cost of Medical Care, Washington, 1929.)

It was estimated that in the United States, in 1932, chronic rheumatic diseases caused a loss of 7,500,000 weeks of work annually and of more than \$200,000,000 to those disabled. In 1931, about 35,000 ex-service men received over \$10,000,000 in disability compensation for arthritis, a number constituting 6.4 per cent of all beneficiaries of the Veterans Administration and a sum constituting 4.7 per cent of all veterans benefits (Matz²¹). These figures are increasing yearly.

Many have called attention to the relatively greater disability from rheumatism than from tuberculosis. In the past 50 years, curves of disability for tuberculosis have fallen sharply, whereas those for rheumatism have risen. Buckley¹⁴ cites the records of a large German medical benefit association to the effect that the proportion of sufferers from rheumatic disability begins to exceed that of tuberculous children who are still of school age, but that by the age of 20 it is more than five times as great. In Germany there is three and a half times as much rheumatism as tuberculosis. Arthritis imposes upon the Swedish Pension Board an economic burden more than twice as heavy as that arising from tuberculosis. More than 12 per cent of its funds are for chronic articular rheumatism. In Sweden, 35,000 persons (0.6 per cent of the total population) are disabled by arthritis, and it is responsible for a yearly cost to the State of six million crowns (about \$1,500,000, Kahlmeter²²). As Copeman¹⁵⁻¹⁶ states, the position of tuberculosis 50 years ago was similar to that of the far more costly, but less dramatic, rheumatic disease today. Tuberculosis has been conquered largely by teamwork between far-seeing laymen and physicians who are determined to rid humanity of such domination. The same result can be achieved in the case of "rheumatism, the Captain of Crippledom."

THE CLINICAL CONTENT OF "RHEUMATISM" IN ITS
BROADEST SENSE

In England, "rheumatism" is a designation generally reserved by physicians for rheumatic fever. For physicians in this country and for laymen everywhere it has much broader implications. It is a term conferred by the layman on a wide variety of conditions, often bearing no other relationship than the common symptom of pain somewhere about a muscle or joint. The physician has been forced to follow suit and has come to use the convenient tag to designate any one of the commoner diseases of joints or muscles. This habit tends to foster cloudiness of thought, and a lack of appreciation of the essential discreteness of these several diseases, of their diverse etiology, and above all of the differences in treatment and prognosis.

While the chief forms of chronic rheumatic disease are atrophic arthritis, hypertrophic arthritis, and fibrositis, their symptoms are in part simulated by a number of other conditions. This discussion will therefore deal with considerably more than these three, and will include notes on progress in many allied disease-states: diseases of joints due to various types of trauma, those diseases associated with chemical or metabolic disturbances such as gout and hemophilia, those due to specific infections (gonorrheal, pneumococcic, tuberculous infections, and so forth), rheumatic fever, fibrositis, or "muscular rheumatism," bursitis and sciatica, atrophic (proliferative, infectious, rheumatoid) arthritis, hypertrophic (degenerative, senescent, osteoarthritis), and a miscellaneous group that includes psoriatic arthritis and neurogenic arthropathies. The maintenance of such a broad viewpoint will counteract one's natural tendency to limit his consideration to "inflammatory rheumatism," "muscular rheumatism," and "chronic arthritis," and to use in every case with joint pain one of these convenient labels. The breadth of the problem should not thus be delineated. Too frequently the subtle differences between a localized, chronic traumatic arthritis, of postural, occupational, or recreational origin, and "chronic osteo-arthritis" are not appreciated. In too many cases gouty arthritis is masquerading under the erroneous diagnosis of acute rheumatic fever or chronic infectious arthritis. The discerning physician will not be satisfied to establish boundaries for "rheumatism" as rheumatic fever in youth, muscular rheumatism and atrophic arthritis in middle life, and hypertrophic (senescent) arthritis in old age.

CLASSIFICATION OF TYPES OF DISEASES OF JOINTS AND RELATED
STRUCTURES AND THEIR PROPORTIONATE FREQUENCY

The following classification of diseases of joints and related structures will serve for purposes of orientation. Its inadequacies are recognized. It omits those diseases of joints which have been assigned more or less by common consent to the orthopedist (e.g. Perthe's disease, osteochondritis dissecans, etc.) or which he has perhaps quietly appropriated for lack of

interest therein by his medical colleagues. This classification, based as far as possible on known or presumptive etiology (for an etiologic classification is the eventual desire), will not satisfy those who insist on one based on demonstrable roentgenologic or microscopic evidence of pathologic change or on one adhering strictly to known facts, nor will it be entirely acceptable to those who, in the absence of full knowledge, insist on using noncommittal terms. It is a working classification, presented without defense or discussion, which seems convenient for this review (table 1).

What is the proportionate frequency of these affections? How alert must the general practitioner be to recognize some of these types, how often is he likely to encounter them? Of the many varieties and species of joint disease noted, less than a dozen will constitute the bulk of one's everyday experience with "rheumatism," even in special clinics. Nevertheless the informed physician will not permit his powers for a more discriminating differentiation to be lulled to rest. If a patient with gout, for example, is found masquerading under the banner of infectious arthritis, the rewards for keenness in diagnosis are great in terms of satisfaction both to the physician and the patient.

The relative frequency of the commoner types varies in different localities because of differences in local conditions of environment, climate, social status, or occupational hazards. Such statistics differ also depending on the type of practice concerned—home, office, or general clinic practice, general hospital practice, or the experience at spas, special clinics, or special hospitals. From his own experience (Rynearson and Hench, 1931) and that of others Hench has estimated that, in general office or general clinic practice, the relative proportions are about as follows. Of 100 people who consult their physician for "rheumatism" * (disease of joints or muscles), there will be approximately 1 case of rheumatic fever, 2 cases of gonorrheal arthritis, 3 to 5 of miscellaneous types (with ulcerative colitis, tabes, or syringomyelia, tuberculous arthritis, psoriatic arthritis, etc.), 3 to 5 of gouty arthritis, 7 to 10 of traumatic (including static) arthritis, 10 to 15 of fibrositis ("muscular rheumatism," diffuse or localized extra-articular "muscular fibrositis," or capsular fibrositis, bursitis, or sciatica), 35 to 40 of chronic atrophic arthritis, and 25 to 30 of chronic hypertrophic arthritis. (Demonstration at meeting of American Medical Association, Cleveland, 1934.)

Of 4,349 patients seen at Bath, Coates and Delicati²³ found that 52 per cent had atrophic arthritis, 16 per cent had hypertrophic arthritis, 25 per cent had fibrositis, and 7 per cent had sciatica. The incidence by sex, males to females, was as follows: atrophic arthritis 9/20, hypertrophic arthritis 9/5, fibrositis 3/2, and sciatica 7/2. In other words, for every 100 women affected by each of the following disorders, there would be 45 men with atrophic arthritis, 180 with hypertrophic arthritis, 150 with fibrositis, and 350 with sciatica.

* That is, whose symptoms are sufficient to take them to the physician. Figures on actual incidence are not available.

Fibrositis seems to be more prevalent in Buxton than at Bath. Classifying 1,496 patients with "rheumatism" at Buxton in four years, Buckley¹⁴ noted that 13 per cent had rheumatic fever, 16 per cent had atrophic arthritis, 16 per cent hypertrophic arthritis, and 55 per cent had fibrositis (including sciatica). He explained the high incidence of the last by the fact that miners and outdoor workers constituted a high percentage of their clientele and were particularly liable to fibrositis, perhaps because the miners, for example, leave damp, fairly hot mines to enter cool air while still wearing hot sweaty clothes. In a further study, limited to men seen three years subsequently, the proportions were found to be about the same: 17 per cent had rheumatic fever, 15 per cent had atrophic arthritis, 15 per cent had hypertrophic arthritis, and 53 per cent had fibrositis. Buckley's figures approximate those of Holt²⁴ at Buxton Mineral Water Hospital, for 1928-1931. Only men were grouped, and rheumatic fever was not included. The proportions in 5,687 cases were: fibrositis 62 per cent, atrophic arthritis 23 per cent, hypertrophic arthritis 15 per cent.

Finally, regarding insured persons, the figures of the Ministry of Health are recalled¹⁰. Among every thousand insured men of all ages there were approximately four cases of rheumatic fever (i.e. one of "acute rheumatic fever," three of "subacute rheumatism"), six cases of muscular rheumatism, ten of lumbago, and three of sciatica (i.e. 19 of fibrositis), one of atrophic arthritis, three of hypertrophic arthritis, three of gout, and one unclassified, a total of 30 affected in each thousand. Among every thousand insured women there were five cases of rheumatic fever (i.e. two of "acute rheumatic fever," and three of "subacute rheumatism"), seven of muscular rheumatism, three of lumbago, and one of sciatic or of brachial neuritis (i.e. eleven of fibrositis), three of atrophic and two of hypertrophic arthritis, gout being practically nonexistent, or a total of about 21 women affected in each thousand.

Each of these and other figures must be considered from the standpoint of the type of practice concerned, as hospital records cannot be compared with those of an insured population, and the latter cannot be compared with those of the general population.

INDUSTRIAL ASPECTS OF RHEUMATISM

Relation of Rheumatism to Worker's Occupation, Age, and Social Conditions. Occupation may have a direct (causal or primary) or indirect (predisposing, precipitating, i.e. secondary) relationship to the appearance of rheumatism. A true occupational rheumatism is one that occurs either exclusively or principally in the given occupation. Even when trauma or some other insulting characteristic of an occupation (exposure to dampness or to thermal extremes) precipitates or aggravates a preexisting rheumatic disease, the resulting rheumatism is not an occupational rheumatism of the direct or primary type. Most so-called "occupational rheumatism" is

TABLE I
Tentative Classification of Diseases of Joints and Related Structures

| Main cause or characteristic | Intra articular | Extra articular | Types |
|---|---|--|---|
| I Trauma | | | |
| (a) Extrinsic (exogenous), generally acute and accidental (Occupational, recreational) | 1 Traumatic arthritis | 1 Traumatic fibrositis ("myositis") | Acute—generally due to single extrinsic trauma, e g "baseball finger" |
| | 2 Traumatic synovitis | 2 Traumatic bursitis, tendinitis, etc e g "housemaid's knee" | Chronic—generally due to repeated minor traumas ("micro-trauma"), e g from obesity, flat feet, scoliosis |
| (b) Intrinsic (endogenous), generally chronic (postural, "static") | | | |
| | | | Acute |
| | | | Chronic |
| II Specific infections (known etiology) generally acute, may be chronic | | | |
| | Intra articular | | |
| | 1 Specific infectious arthritis | | (1) Gonorrheal |
| | 2 Specific infectious synovitis | | (2) Tuberculous |
| | | | (3) "Septic joints" staphylococcal, pyogenic streptococci |
| | | | (4) Pneumococcal |
| | | | (5) Typhoidal |
| | | | (6) Syphilitic (spirochetal, not arthropathy) |
| | | | (7) Miscellaneous and exotic, with Malta fever, dengue, dysentery, leprosy, yaws, malaria, with infection by <i>B. coli</i> , <i>B. dysenteriae</i> , <i>B. influenzae</i> , meningococci |
| | Extra articular | | |
| | 1 Specific infectious fibrositis, e g trichiniasis, psoas abscess | | |
| | 2 Specific infectious bursitis, e g syphilitic bursitis | | |
| III "Nonspecific" infections (of unknown etiology) possibly (or probably) related to infection, focal "streptococcal (?)" or their toxins (?) | | | |
| | Intra articular | | |
| | 1 With rheumatic fever—(diffuse, articular, and extra-articular) | | |
| | 2 With "specific ulcerative colitis" | | |
| | 3 With scarlet fever | | |
| | 4 With certain skin diseases psoriasis, erythema nodosum, scleroderma, lupus erythematosus, peliosis rheumatica | | |
| | 5 Atrophic arthritis including atrophic spondylitis | | |
| | Synonyms rheumatoid, proliferative, "nonspecific infectious," "infective," spondylitis ankylopoietica, etc | | |
| | Extra articular (May occur alone or with above) | | |
| | 1 "Infectious (?) fibrositis" | | |
| | a Capsular "periartthritis," "periarticular fibrositis" | | |
| | b Muscular localized (e g lumbago, torticollis) or diffuse "muscular rheumatism" | | |
| | c Bursal e g subacromial bursitis | | |
| | d Perineural e g sciatica of certain types | | |
| | e Tendovaginitis e g Dupuytren's ganglion | | |
| | 2 Rare forms of myositis (ossificans, fibrosa, etc) | | |

TABLE I—*Continued*

| | | | | |
|------|--------------------------------|-------------------------------|---|--|
| IV | Degenerative changes in tissue | Intra-articular | 1 Hypertrophic arthritis, including hypertrophic spondylitis Synonyms degenerative, senescent, osteo arthritis, spondylitis osteo arthritis <i>a</i> Fingers Heberden's nodes <i>b</i> Knees with "static arthritis of obesity" <i>c</i> Spine "hypertrophic spine of elderly" <i>d</i> Hips morbus coxae senilis <i>e</i> Shoulder usually a bursitis or peri-arthritis rather than arthritis 2 Arthropathies <i>a</i> "Charcot joint"—secondary to lesions of central nervous system <i>b</i> Tabes dorsalis, syringomyelia <i>c</i> Pulmonary osteo arthropathy—secondary to lesion of lung Extra-articular Fibrositis (muscle pains and stiffness) Bursitis (subdeltoid), often associated with "hypertrophic arthritis" | V Chemical, metabolic or "endocrine disturbance" (Some would also place either atrophic or hypertrophic arthritis, or both here) |
| | | | | |
| V | | Intra-articular | Probably chemical <ol style="list-style-type: none"> 1 Gouty arthritis 2 Hemophilic arthritis 3 Arthritis of serum sickness (true allergic arthritis) 4 With ochronosis 5 Joint changes (minor) with acromegaly { Diseases essentially osseous, not articular 6 Joint changes (minor) with parathyroidism { Possibly chemical <ol style="list-style-type: none"> 1 Intermittent hydro-arthritis Entities not fully established 2 "Allergic arthritis" from food 3 "Climacteric arthritis"—"arthritis of the menopause" 4 "Endocrine arthritis"—various types ovaripriva A Thyreopriva, "villous synovitis," and so forth Extra-articular Some would add various myalgias with lead, thyroid, excess alkalis, bismuth, arsenic, and so forth | VI Neoplastic |
| | | | | |
| VI | | Articular | 1 Primary, generally benign e.g. chondromatosis 2 Secondary malignant, metastatic | |
| | | | | |
| VII | | Articular and extra-articular | 1 "Mixed types" of arthritis 2 Unclassifiable types 3 Functional types, e.g. "hysterical joints", myalgia of fatigue and exhaustion | |
| | | | | |
| VIII | | Miscellaneous | | |
| | | | | |

of the indirect or secondary type, the occupational hazards merely providing contributory factors, nonetheless important. Danischevsky²⁵ has estimated that, in any one year, 4 per cent of all Russian workers become temporarily incapacitated from rheumatism, with an average yearly loss of 48 days' work.

The factor of the worker's age increases the liability tremendously, as Thomson²⁶ and Fischer²⁷ emphasize. Seventy-five per cent of industrial workers over 40 suffer from some type of rheumatism. Thomson, in a survey of 500 cases of industrial accidents, found that arthritis was present in 95 cases, or 19 per cent. In 49 per cent of these cases arthritis had its onset with, or was aggravated by an injury, either occupational or causal. One-half became compensation cases. Persons more than 30 years of age who are employed in farm trade or at labor are particularly susceptible to the development of arthritis following injury. This susceptibility increases with age. Though an injury is often blamed for arthritis, Thomson was of the opinion that it may often be only an incidental factor, as other inciting and predisposing factors are also operative. However, the compensation act of Nebraska (and of certain other states) has been so interpreted as to include arthritis in benefits when proof is offered that the arthritis was the result, or a complication, of trauma, or has even been aggravated by trauma. Thomson concluded that a man over 40 years of age is a considerable liability both to his employer and to his insurance company, and that the older he gets the greater risk he becomes. This presents a problem for medical economics.

New surveys on industrial rheumatism are available (Buckley,^{14, 28} Kahlmeter,²⁹ Fischer,³⁰ Coates and Delicati,²³ and Fox^{9, 12}). Outdoor occupations were associated with considerably more industrial rheumatism than indoor occupations. Tempelaar and Van Breemen (1931), found that of 3,000 patients, those with outdoor employment had three to five times as much rheumatism of various types as indoor workers. Of 1,931 men seen at Bath who were affected with various types of rheumatism, two-thirds were engaged in open air occupations. The occupations in which rheumatism is especially prevalent are those entailing exposure to excess heat (metal workers, bakers), to dampness (dyeing and textile workers, miners, refrigerator workers, bath attendants, and window and bottle washers), and to extremes of weather (carpenters, farmers, laborers, postmen, locomotive engineers, policemen, chauffeurs, conductors, forestry workers, and ship builders). As previously noted, miners seem particularly liable to fibrositis. 71 per cent of 452 miners were treated for this complaint at Buxton, as compared to 45 per cent of 1,044 persons of other occupations (Buckley¹⁴).

Atrophic arthritis is not associated with occupational strain nearly as often as hypertrophic ("osteo-") arthritis. Among 1,114 workers Fischer³⁰ found that only 1 per cent had atrophic arthritis, whereas 48 per

cent showed "degenerative joint changes" Although his data convinced him that the "deforming arthropathies" originate most frequently from static, functional, and traumatic causes, Fischer does not believe that occupational injuries alone very often produce the arthropathy but that a constitutional disposition is the deciding factor Freund³¹ is of the same opinion

In Sweden there is more invalidism from "chronic articular rheumatism" in the country, than in towns and cities The lowest incidence was in large cities The greatest invalidism is among landworkers and peasants²⁹ In Russia also, villagers are said to be thus affected twice as often as those in cities (Danischevsky²⁵) In Germany, arthritic invalidism is at a minimum where working and housing conditions are good (Edstrom³²)

The general conclusion of a discussion, led by Warner,³³ on the relation of soil and climate to rheumatic diseases was that climate is not the prime cause of rheumatism, but that climate has an effect on people subject to rheumatism

DISEASES OF JOINTS RELATED TO TRAUMA

Traumatic Arthritis General Considerations While fibrositis and atrophic arthritis can be produced indirectly (precipitated or aggravated) by occupational trauma, Fischer²⁷ was of the opinion that hypertrophic arthritis is the only form of arthritis for which mechanical trauma is solely or mainly responsible, and that this true occupational arthritis generally only involves shoulders, hands, and especially elbows The "deforming arthropathies" of the hip, knee, and feet, he believes, are caused more by static influences than by occupation

The results of trauma to articular and periarticular structures depend largely on the type, severity, and duration of the injury Due to variations in resistance (the factor of constitutional predisposition), joints may react differently to identical trauma In one case a temporary, perhaps minor, disability and rapid healing results, in another case chronic arthritis may eventuate The varieties of injury which affect joints are in general due to (1) accidental, (2) recreational, (3) occupational, and (4) postural trauma Accidents, such as blows and falls, provide an acute exogenous (extrinsic) trauma Recreational and occupational hazards may result in either an acute (gross) or chronic (micro) trauma Postural or static defects provide the basis for an endogenous (intrinsic) chronic trauma

There is no difficulty in recognizing an acute traumatic arthritis or peri-arthritis, but when the onset of joint disability is insidious and its course chronic, its connection with repeated minor injury may be forgotten or may seem too remote for consideration The rôle of trauma may then be missed entirely It is difficult to determine the interval within which an arthritis may be considered the result of a single injury In half of 48 cases studied by Thiem³⁴ the joint trouble began within eight days, but in others the interval was four weeks and in two cases it was three months and six months

respectively. As to the results of repeated minor trauma, the earliest occurrence of a deforming arthropathy after starting the responsible occupation was three years, and the latest was 30 years (Fischer³⁰). Various types of work induced the same type of deformity, and no particular relation existed between the severity of the resultant joint injury and the length of time in which any particular work was pursued. Hence the factor of individual susceptibility or constitutional predisposition seemed crucial. Fox^{9,12} repeats the warning of Weisz³¹ that a single strain or contusion may be followed by years of pain and limitation of motion even with no obvious anatomic change. Atrophy of muscles may ensue, and the whole body may be affected by a traumatic neurosis. Hence all employers should have treatment instituted promptly, early use of heat and movement, with adequate physical and roentgenographic examination to lessen the demand for compensation benefits and the chances of neuroses.

To study the response of articular structures to injuries of various sorts, Key³⁶ resected a rectangular portion from the patellar aspect of the femur, hypertrophic arthritis resulted. A similar type of arthritis was produced by various chemical insults to cartilage. Articular cartilage is the most vulnerable tissue of a joint, and if it is injured in any way and the joint continues to function, the result is hypertrophic arthritis regardless of the type of injury.

Others also have produced hypertrophic arthritis in animals by various kinds of injury to joints. The results are difficult to interpret, according to Doub,³⁷ who favors reliance on clinical opinion that tends to show that a severe single, or a mild but repeated type of injury can and does produce the picture of hypertrophic arthritis. According to Doub opinions are divided as to whether injury can aggravate an already existing arthritis. (To us it seems well established that it may—Ed.) To establish the diagnosis of a true traumatic arthritis Doub insisted that there must be proof of an injury and exact information regarding its severity, the injury must have been applied to the joint in question, information must be obtained as to the previous function of the joint in question, the time interval between the injury and the occurrence of pathologic changes must be within the generally accepted limits (a few months to a year), and there must be clinical and roentgenologic evidence of pathologic changes in tissue. The roentgenologist, however, can only report the presence or absence of pathologic deviations present in the films and clinical signs are more important. Roentgenologic evidence alone can not decide the question. If in cases of pre-existing arthritis it is decided that a traumatic arthritis also exists, compensation should be paid only until the previous state of use of the joint has been restored. Unfortunately, as Cotton³⁸ points out, the determination of the previous state of the joint may be difficult to make, since as a rule there has been no clinical or roentgenologic examination made before injury.

Effect of Fracture on Articular Cartilage The mechanism whereby joint cartilage is repaired following injury or disease is not fully understood

Repair differs where perichondrium is present. The central part of articular cartilage has no perichondrial covering. Reparative processes in this area are said to be characterized by the fact that no new formation of cartilage from proliferating cartilage cells occurs, and defects of cartilage may or may not undergo cartilaginous repair. Where, however, the defect involves the underlying cancellous spaces, a sluggish formation of new cartilage is seen, resulting from metaplasia of the connective tissue cells of the exposed cancellous areas.

Under certain conditions, such as that seen in articular cartilage of the hip joint following complete intracapsular fracture of the neck of the femur, Santos³⁹ has demonstrated that, if the blood supply remains intact, articular cartilage may first undergo degeneration, then resorption, as the result of invasion of cartilage from subjacent bone marrow, and thirdly, regeneration from active formation of new hyaline cartilage, in part from overlying vascular pannus of fibrous tissue but to a greater extent from a proliferation of surviving cartilage cells. The invasion of cartilage from subjacent bone marrow is like that seen in some cases of arthritis deformans. Where the trauma caused an interruption in vascular supply, such processes of cartilage repair do not occur. The femoral head becomes necrotic, and invasion of articular cartilage from subchondral marrow and proliferation of cartilage cells does not result.

Traumatic Rheumatism, Specific Types. Some of the common designations for traumatic disease resulting from occupational and recreational injury to joints are the "glass arm" of musicians and ball players, "golfer's arm," "motorist's arm," "soldier's shoulder," "tennis elbow," "miner's elbow," "tennis-player's wrist," "baseball fingers," "engineer's spine," "farmer's back," "tennis back," "driver's thigh," "cyclist's thigh," "weaver's bottom," "nun's or housemaid's knee," "rider's knee," "game knee," "tennis leg," "fencer's bone," "dancer's bone," "nurse's feet," and "policemen's heel." Similarly, various muscular affections are recognized and designated as "writer's, waiter's, auctioneer's cramp" and so on.

A pathologic basis for some of these conditions has not been exactly defined. In some instances they represent not one entity but one of several affections. The underlying condition in "glass arm" is usually thought of as a subdeltoid or subacromial bursitis (with or without involvement of the capsule of the shoulder joint or calcification of the supraspinatus tendon). Others, however, define it as a "neurosis marked by spasm of the pronator teres muscle." "Driver's thigh" is generally considered to be a postural sciatica, "weaver's bottom," a bursitis at the ischial tuberosity, "housemaid's knee," a prepatellar bursitis, "tennis player's wrist," a tendovaginitis. Affections of the shoulder are common in several occupations: in stokers from shovelling, gardeners from digging, miners from hewing, chauffeurs who use a hand brake, plasterers who must wield trowels at the height of their heads, and workers with compressed air tools (Ray,⁴⁰

Fischer,³⁰ Freund³¹) The constantly repeated vibrations of the pneumatic drill may produce eventual splitting and destruction of articular cartilage

"*Tennis Elbow*," *Epicondylitis Humeri*, *Radiohumeral Bursitis* Tennis elbow, according to Carp,⁴¹ may represent either an inflammatory involvement of the conjoined tendon (of the extensors) at the lateral epicondyle of the humerus, or of a structure in close proximity thereto, such as the radiohumeral bursa The term is a misnomer, as the condition it represents may occur not only as a result of sports requiring the use of a tennis or squash racket, but of others such as golf, polo, and baseball, and also of occupations demanding lifting and sudden flexion and extension of the elbow, such as are required of clothes pressers, violinists, blacksmiths, telephone operators, salesmen carrying grips, and housewives Its cause may be chronic trauma or acute injury over the lateral aspect of the elbow It is frequently diagnosed as a "sprain" or as "rheumatism" Its symptoms may appear acutely, or be chronic and mild There are pain, tenderness, and sometimes swelling and heat in the region of the epicondyle The pain may be of a sudden, sharp, darting character, causing a quick cessation of the movement producing it, or it may be dull and constant, radiating to the arm, forearm, or hand Extension of the elbow, pronation, supination, or tight flexion of fingers may increase the pain Extension of the wrist may relieve it Weakness of extensor muscles of the forearm is usually present, with a weak hand-grip (According to Hansson, 1930, passive motion of the elbow, forearm, and hand may be quite painless and free, as is active motion of the flexors when the forearm is supinated—Ed.)

Since Bernhardt's first description of it (1896) as a neuralgia, others have considered tennis elbow to be due to periostitis of the epicondyle, a myofascitis of the extensor muscle at the external condyle, a radiohumeral bursitis, an arthritis of the radiohumeral joint, a tear in the extensor carpi radialis longus, an affection of the supinator brevis muscle, an involvement of the capsule of the elbow joint or of the subcutaneous fat, fascia, and periosteum of the epicondyle, a malalignment of the radial head and of the lower end of the humerus, or "adhesions" Osgood described it as a radiohumeral bursitis (Osgood-Allison, 1931) In Carp's study of eight cases roentgenograms showed a cloudy, distended, frequently calcified, radiohumeral bursa and at times an osteitis of the epicondyle The treatment of choice was to rupture the bursa by firm digital pressure, applied over the epicondyle and radiohumeral joint Prompt, often dramatic, relief may be expected Resorption of calcium follows In some instances conservative treatment consisted of heat and rest The forms of treatment advocated by others (manipulations, splints, roentgen therapy, infiltration with procaine) are considered less useful Excision of the bursa is not recommended unless manipulative rupture, or rest and heat, fail to give relief One calcified bursa was removed and the pathologic changes were described

"*Chauffeur's Shoulder*" In connection with London busses, rheumatic affections seem to be the special hazard for both man and beast We have

been told of the localized exostoses and injured cartilages seen in London cab horses (Buit, 1928) Nairn⁴² has now described an osteo-arthritis of the shoulder joint of London busmen, the etiology of which he believes to be trauma from gear shifting and not from exposure to inclement weather as one might at first assume. In busses, gears are generally stiff, to change them requires considerable effort and jarring. Among busmen driving the older buses, with right hand gear-shifts, the arthritis affected the right shoulder joint, for those driving new busses, with left hand gear-shifts, the left shoulder was involved. Diathermy and massage gave relief.

"Driver's Thigh" A neuralgia of the sciatic nerve may occur among those who drive motor cars continually. The symptoms, according to Hoets,⁴³ may vary from an ill defined feeling of fatigue of the thigh muscles, to those of classic sciatica. The cause of the sciatica is the continued use of the accelerator pedal, the leg being held in one position for long periods. Hoets has given diagrammatic evidence of the relation of faulty seats to this condition. If the driver sits badly, or if the rear springs of the seat have given away, an abnormal tilt may engender unusual pressure and eventual injury to the sciatic nerve just before its division in the lower third of the thigh. Treatment consists of the proper adjustment of the faulty seat.

Titus⁴⁴ stated that serous effusions are dissipated from joint cavities not by blood channels but by means of lymphatics. Therefore, in cases of traumatic synovitis one must not expect great results from diathermy, although some relief of pain may be afforded. Some forceful mechanical influence, such as massage above the knee and up the thigh, is required to encourage the forcing of the effusion into the lymphatics. (Considerable experimental evidence exists, however, that effusions are in part dissipated via blood vessels—Ed.) Heat is indicated preliminary to massage. Diathermy will not heat the inside of the knee, and a heat lamp will suffice. Titus favors the use of static currents, and claims that fluid can generally be removed in three or four treatments by "the obvious decongesting action" of high-voltage currents provided by the static brush discharge. An ace bandage in a "figure of eight application" is used in the interval between treatments.

Hemarthrosis Simple traumatic hemarthrosis at times necessitates aspiration to remove blood and fluid in order to prevent formation of disabling adhesions which Key and others have shown may result from experimental as well as clinical hemarthrosis. Even so, repeated aspirations may be necessary and convalescence prolonged. The injection of air into joints after aspiration has, according to Johnson,⁴⁵ hastened recovery and given prompt relief of pain. Thirty-two cases so treated escaped complications or permanent disability.

Traumatic Bursitis and Ganglion Formation Three patients with acute exacerbations of chronic prepatellar bursitis, presumably due to trauma, were treated by Diamond⁴⁶ by aspiration of bursae and injection of 5 c c of tincture of metaphen, 1:200. Rapid reduction of swelling and apparently con-

plete occlusion of the bursal sac occurred, with no recurrence after 11 to 20 months. One must be sure that the bursa does not communicate with the knee joint, as such fluid would cause injury thereto. When adhesions in bursae have caused sacculation, an injection of each sac is necessary.

A very large bursa, placed over the ischial tuberosities and analogous to "weaver's bottom," was removed by Fraser⁴⁷ on the assumption that it was a lipoma. It weighed 2 pounds 10 ounces, its circumference was 18½ inches, and its diameter 6½ by 6 inches. •

A ganglion is a cystic swelling which contains thick mucoid matter. It usually has a thin wall and occurs in the region of the capsules of joints or tendon sheaths. The cause of such ganglions is unknown, although trauma seems to be an important agent. They occur more often among women than men, and more often in the hands and feet, especially in relation to the capsule of the wrist. E. S. J. King⁴⁸ has described the three stages of their development: (1) marked proliferation of spheroidal cells, with mucoid material in and between the cells, (2) similar cells in the wall of a cavity containing mucoid material, and (3) a well-defined cavity and a well-formed wall containing spindle cells.

Industrial Backache The correct diagnosis and disability-assessment of the "industrial back" is an almost daily requirement of the "company physician" and the orthopedist. Such backaches provide a problem of great economic importance. Confusion concerning their differentiation results from lack of complete understanding of the anatomy and pathologic physiology of the spine, and from the misconception that the spine is an especially strong structure, immune to most of the conditions that beset other joints. Until recently the weaknesses inherent in the back, so obviously revealed since man began the experiment of walking on two instead of four legs, have not been fully appreciated. The spine is a flexible structure basically similar to an arm or a leg, with its units, the vertebrae, made up of the same structures as a knee or ankle. Kidner⁴⁹ emphasized the fact that joints of the spine are subject to the same ills as other joints, traumatic or infectious synovitis, or that secondary to fracture, sprains, overstretching or rupture of ligaments, effusions and adhesions, strains, overstretching of contiguous muscles, infectious or traumatic arthritis and minor as well as major fractures. Affections of muscles are probably the most common cause of backache. They become flabby, relax, and lead to unstable articular apposition, bad posture, and chronic strain. They are subject to strain, fatigue, rupture, or inflammation. Intervertebral disks are susceptible to injury or to disease. The nerves, as they leave the spine, are extremely liable to irritation or pressure.

Kidner has reviewed the common types of industrial backache, and summarized the symptoms and signs whereby injuries to the back can be recognized. The following are the more frequent types of disturbance: 1. Injury to the fibers of the erector spinae muscles, such as may occur when a man carries a heavy weight, and which is characterized by sudden pain

that then lessens only to increase and keep its victim bedfast the next day

- 2 Strain at the lumbosacral or sacroiliac joint, sprain of these joints, so liable to injury, should be considered as presenting the same problem as sprain of an ankle, i.e., tearing of ligaments, hemorrhage in periarticular tissues, possibly effusion into the joint, pressure on nerve roots, and consequent pain
- 3 Crushed or impacted fracture of a vertebral body may occur after only slight trauma, it is commonest at the dorsolumbar junction and is frequently overlooked when a lateral roentgenogram is omitted
- 4 Injuries of the intervertebral disks are less frequent causes of backache. Roentgenograms may show a bulging hernia of the nucleus pulposus through the annulae fibrosus. Laminectomy for the relief of pressure may be necessary if the hernia enters the vertebral canal and produces pressure on the cord. If it pushes through the bony plate of the adjacent vertebral body in the spongy bone, the moderate pain may be relieved by rest and a back brace
- 5 Spondylolisthesis is probably due to a congenital failure of union between the normal anterior and posterior centers of ossification of the arch of the vertebra. This permits the vertebral body to slip slowly forward, with stretching of the cartilaginous union under the strain of weight bearing. It is often a chance finding in otherwise normal persons. When first discovered, after a back injury, its appraisal is difficult and its presence increases difficulties in treatment

While acute backaches incident to industrial trauma generally disappear with reasonable treatment, neglected cases become great problems. Persons afflicted present the syndrome of pain, which prevents working, stooping, lifting, and sometimes standing or walking. The syndrome results from real pathologic changes, habit pain, the sympathy of relatives, or the chance of disability compensation. Malinger and overstatement must be recognized, but it is even more important to recognize the undoubted evidences of pathologic changes that may be present: real protective muscle spasm, real sensitivity to pressure over the lesion, limitation of movement but only to the degree appropriate to the suspected lesion, constancy of symptoms and signs, and above all adequate roentgenographic data and, when indicated, a neurologic examination. A prerequisite to successful treatment is the patient's desire to get well. Kidner has outlined the treatment of his choice: rest, sometimes for several weeks in bed, and at times in a cast, other orthopedic appliances, as necessary, and the appropriate types of physical therapy.

Prevention and Treatment of Industrial Rheumatism Measures suggested for the prevention of various types of rheumatism incident to industry are summarized in a recent symposium (Fox,^{9 12} Neligan,¹⁰ Copeman,^{15 16} Boyd¹³). Miners should wear light working clothes to permit aeration and minimize stagnant sweat. Before facing changes in temperature outside the mine, they should bathe at the mine head and change to warm, dry clothing. Workers in cold places should be provided with insulated clothes, especially boots and leather pads, warm canteens, hot food, and hot foot-baths. For those exposed to wet, waterproof clothing, warm

boots, and warm dressing rooms are essential. In all occupations in which there is excessive perspiration an abundance of bland drinks, such as oatmeal or barley, is desirable. The joints and muscles of workers, e.g., drillers who are subject to prolonged vibration or other trauma, should be protected by shock insulators, leather pads, or other devices. There should be pauses from fatiguing work. Predisposing factors of industry aside from trauma should be minimized by the avoidance of damp offices and houses, adequate sunshine, proper hours for food and rest, and reduction of avoidable mental and physical strain. Social workers can do much to investigate, correct, and control such phases of the problem.

The British insurance physician is handicapped in that although he can guarantee the victim a pension, he cannot set machinery in motion for his admission to a spa hospital or to special clinics for physical therapy. Rapid return of the patient to industry and the avoidance of progressive deformity and disability usually necessitate more special care than the physician can provide the patient who is confined to his home. While more "rheumatism units" and "special physical therapy centers" are being established, it is imperative that they be made available to the indigent worker whose dole so far covers little more than maintenance and does not provide for prolonged treatment. When treatment can be begun early, great disability can be prevented. By evening physiotherapy sessions, many can be kept at work during the day (Ray⁴⁰). The patient's occupation may have to be changed. Fox listed as those occupations least harmful to an existing rheumatism office work of various kinds, teaching, library or laboratory work, seamstress, telephone exchange, book binding. The tobacco business is especially favorable, as cigars must be kept in a warm dry atmosphere.

DISEASE OF JOINTS DUE TO INFECTIONS OF KNOWN TYPE

Acute Pyogenic Arthritis, "Septic Joints" Although the treatment of acute suppurative arthritis ("empyema of joints," "acute epiphysitis") is generally surgical, diagnosis and preoperative care are a medical problem. Its causes, diagnosis, and treatment have been reviewed by Caldwell,⁵¹ Bisgard,⁵² Sevier,⁵³ and Foster.⁵⁴ It most frequently affects the joints of children, the hip especially, less commonly the knee, ankle, sacro-iliac region, shoulder, elbow, or wrist. "Septic arthritis" arises in three ways: (1) from a hematogenous infection localizing in a synovial membrane, (2) by extension from a hematogenous type of osteomyelitis from bacterial infarction, affecting closely contiguous or intra-articular bone, and (3) infrequently, from penetrating wounds of joints.

Common types of infection responsible are otitis media, umbilical infection, scarlet fever, tonsillitis, the "ordinary sore throat" (Sevier⁵³), gonococcal and pneumococcal infection, and those after circumcision. Symptoms are sudden onset of high fever, leukocytosis, and pain and tenderness in the involved joint. When a hip is affected, a characteristic

position is assumed, due to muscle spasm, namely, flexion, with either abduction and external rotation or adduction and internal rotation. The latter favors spontaneous dislocation of the femur. Pain may be referred to the lower thigh, knee, or calf, but passive motion of the knee is painless and that of the hip is very painful.

For the first 10 or 15 days, roentgenograms are usually negative and no bony change is visible, although after five or ten some narrowing of cartilage space may be visible. When a diagnosis of pyogenic arthritis is suspected, one should not rely on a negative roentgenogram but should early perform diagnostic aspiration. Aspiration, and even exploration, will do no material harm in cases of nonseptic arthritis, but if delayed in cases of pyogenic arthritis, extensive and irreparable injury may result (Foster⁵⁴). If pus is obtained on aspiration, immediate surgical drainage may prevent further destruction of cartilage by proteolytic enzymes from the leukocytic exudate. Muscle spasm is then relieved by fixation and traction. (Surgical drainage is not indicated in every case of septic arthritis, it depends on the degree of sepsis and the patient's reaction. Some cases, such as the gonorrheal type, may respond well to aspiration and washing, without need for more extensive drainage—Ed.)

The course and prognosis depend on the nature and site of the articular infection. If articular sepsis arises from infection localizing in synovial membrane, the cartilage may be destroyed but adjacent bone is seldom invaded, the prognosis is then good, nearly normal function frequently being restored. If sepsis arises from infected foci in adjacent bone, however, such as from osteomyelitis of the neck of the femur, femoral epiphysis, or pelvic bone, destruction of bone occurs, the synovial membrane and cartilage are invaded secondarily, the latter being destroyed, and ankylosis or pathologic dislocation of the head of the femur is the usual sequel. (Phemister is of the opinion that epiphyseal infection is much less common than diaphyseal infection.)

At aspiration or surgical drainage one cannot always be certain from whence the infection arises. If fever subsides and prompt improvement is noted, the local origin of infection is usually in synovia. If fever fails to subside within 10 days, a source of bone infection must be suspected, roentgenographic examinations must be repeated and, if infected bone is found, drainage must be performed. Bacteriologic studies usually reveal *Staphylococcus aureus*, pneumococci, or streptococci. Such studies are helpful, as Beekman and Wilensky⁵⁵ (cited by Bisgard) reported that staphylococci usually signify infection of contiguous bones, whereas infection with pneumococci or streptococci generally results from blood-borne metastatic infection affecting synovia.

Caldwell⁵¹ studied cases of septic arthritis in which 18 hips (of 17 children) were affected. In six hips a hematogenous infection had localized in synovia, in 12 hips intra-articular infection arose from adjacent osteomyelitis. One of the children with a septic synovitis died of septicemia. Results in

the 16 cases in which children survived (17 hips being affected) were as follows normal or nearly normal motion was restored in eight hips, in five of which there was chiefly synovial inflammation and in three infection from osteomyelitis. Partial or complete ankylosis resulted in the nine additional cases of sepsis secondary to osteomyelitis, four with solid ankylosis and five with pathologic dislocation and limited motion. The average duration of illness before operation was 13 days, the average stay in the hospital two and a half months.

Of 217 cases of pyogenic osteomyelitis Bisgard⁵² noted an associated septic arthritis in 51 cases (24 per cent) in 42 of which it arose by direct extension from an adjacent diaphyseal infection. In nine cases the joints appear to have been involved by hematogenous infections, presumably from remote foci of osteomyelitis. Only 13 per cent of joints infected by direct extension regained a good range of motion, 65 per cent became ankylosed, and the rest suffered varying degrees of functional limitation. A third of those infected from distant sources regained a good range of motion and 65 per cent developed ankylosis, the rest obtained variable limitations.

Gonorrheal Arthritis and Synovitis Gonorrheal arthritis is the most common form of joint disease of known infectious origin. Of 13,000 patients with gonorrhea seen by Lees,⁵⁶ 388 or about 3 per cent (3.2 per cent males, 1.8 per cent females) developed gonorrheal arthritis. Contrary to experience in this country arthritis did not complicate any of the 150 cases of gonorrheal vulvovaginitis in children. McCahey,⁵⁷ who has written a short account of the literature on this disease, believes that urethral trauma, trauma to the joint, and previous rheumatic arthritis do not predispose to the development of gonorrheal arthritis.⁵⁸ According to him, infected seminal vesicles are a more common focus than prostatic infection, metastatic infection "occasionally" arises from the anterior urethra.

Lees classified acute joint involvement with gonorrhea as follows: (1) arthralgia of one or more joints, (2) acute synovitis, (3) acute arthritis, in which cartilage, synovia, capsule, and periarticular tissue are involved and a serofibrinous exudate is present, and (4) acute purulent arthritis, a rare complication which may result from gonococci alone and not necessarily from a mixed infection. Subacute and chronic cases may be of two types: (1) synovitis, (2) arthritis with involvement of cartilage, synovia, and periarticular structures.

An arthralgia may represent merely a toxic reaction. When joint exudates arise, actual articular invasion with gonococci has occurred. In 80 per cent of Lees' cases of gonorrheal arthritis joint manifestations occurred within the first four or five weeks of the primary infection. It was seen as early as the fifth day in a case of urethritis, in chronic genito-urinary infections the onset of arthritis may be later. Arthritis has been recorded as having occurred 15 or 20 years after the onset of gonorrhea, generally having been induced in such cases by instrumentation or pelvic surgery.

Only 15 per cent of Lees' cases were monarticular, 85 per cent were polyarticular. The order of frequency of involvement was knee in 64 per cent, ankle in 37 per cent, metatarsophalangeal joints in 35 per cent, shoulder in 23 per cent, wrist in 14 per cent, metacarpophalangeal joints in 14 per cent, elbow in 2 per cent, hip in 4 per cent, intervertebral joints in 3 per cent, and temporomandibular joint in 2 per cent. Sternoclavicular joint involvement was not noted, an area involved in 2 to 3 per cent of cases according to the statistics of others.

The symptoms of gonorrheal infection of joints are variable depending on the virulence of the infecting agent and the resistance of tissues. An acute arthritis of one or more joints may follow a few days of fleeting arthralgia. The temperature may be 101 to 103° F. Pain, sweating, and fluctuations in joints are more marked in those rare cases where actual suppuration occurs. Lees agreed that roentgenographic changes in gonococcal arthritis are not diagnostic. In 72 cases of gonococcal arthritis Delacroix⁵⁹ noted decalcification of bone-ends and a rarefying osteitis proceeding to destructive ankylotic changes. A severe arthritis may accompany a "mild gonorrhea."

With roentgenograms taken of air-filled joints, in two cases of acute gonococcal synovitis in which experimental pneumo-arthritis were produced, Ginsberg⁶⁰ followed the sequelae of effusions and noted characteristic adhesions in the suprapatellar pouch responsible for later mild stiffening. The effusion, which escaped absorption or aspiration, became static in different portions of the suprapatellar pouch and the joint proper, and became organized.

A positive complement fixation test to gonococci is considered by Lees and by Green⁶¹ to be of great value, it was positive in 75 to 80 per cent of Lees' cases. A negative test, however, does not exclude gonococcal causation. The sedimentation rate is rapid, as in acute rheumatic fever and atrophic arthritis. It is of little value in differentiating various forms of arthritis, but repeated tests are helpful in gauging the activity of the process during the course of the disease. (Oppel, Myers, Keefe⁶²)

Treatment of Gonorrheal Arthritis. Treatment must be general, to the original focus of infection, to infected joints, and for the septicemia or pyemia. Lees⁵⁶ discussed the value of various forms of therapy: rest, diuretics, medicines, prostatic massage, urethral irrigations, foreign protein therapy, and various forms of physiotherapy. In the acute stage, heat, rest, and immobilization are indicated, but movement and massage must be instituted as soon as possible to prevent permanent loss of motion (Lees, Ginsberg). The effects of high-frequency currents (diathermy) to prostate gland and vesicles, as introduced by Cumberbatch and Robinson, have been disappointing to Lees who advocates "specific therapy" with "detoxicated vaccines." Delacroix is convinced of the value of radioactive mineral waters in restoring normal calcification to the affected bones.

Conservative (i.e., nonsurgical) measures are favored except in pyar-

throsis, in which case arthrotomy is advocated (Lees,⁶ Neely⁷³) The value of irrigation is noted with bichloride solution (LeBreton⁶⁴), with Pregel's solution (Thomson⁶), and with warm saline solution Ginsberg felt that benefit resulted from injections of an

The method of treatment that bids fair to supplant all others for gonorrheal infections, especially of joints, is hyperpyrexia by "superdiathermy," radiothermy, or hot air-conditioned cabinets Since 1931 brief reports have appeared indicating that rapid sterilization of joints and the genito-urinary tract can be accomplished if by these means the patient's temperature can be elevated long enough to reach or exceed the thermal death point of various strains of *Neisseria gonorrhoeae* The thermal death time of fifteen or more strains of gonococci in vitro has been determined as about 5 hours at 41° to 42° C (Carpenter, Boak, Mucci, and Warren⁶) A few strains are more resistant and need the same temperature for longer periods or a higher temperature for shorter periods Carpenter and Warren treated patients with gonorrheal arthritis with radiotherapy and superdiathermy Patients were "usually cured," although in one case there was complete failure after seven hours of heat at 41.5° C In this case the thermal death point of the gonococcus isolated from the joint was much higher than the amount of fever induced in the patient Nine patients were treated by two fever sessions of five hours each with "very encouraging results" by Bishop, Horton and Warren⁶⁷ Acute arthritis subsided rapidly, redness and tenderness disappeared, and mobility was gradually restored Chronic arthritis became painless and there was gradual relief from stiffness Tenney⁶⁸ believed that if a temperature of 106° F is maintained for two to four hours, it acts almost as a specific against gonorrheal arthritis, as he believed the thermal death point of the organism to be about 104° F In two cases in which the patients were treated by Warren and Wilson⁶⁹ symptoms subsided entirely after one or two sessions of fever at 41.5° C for five hours

A patient of Berris⁷⁰ with acute gonorrheal arthritis received no relief after four treatments each at 103° F for four hours, but a patient with "probable gonorrheal arthritis" of six months' duration obtained "complete relief" after six treatments at 102° F for three hours Simpson, Kishig and Sittler⁷¹ obtained gratifying results in the treatment of gonococcal and other types of infectious arthritis using radiothermy and later an improved hot air-conditioned cabinet Atsatt and Patterson⁷² treated eight patients with gonorrhea of the joints and genitals by general diathermy In all eight cases the arthritis was cleared by one to five treatments, at temperatures not over 103.5° F, for periods of five hours or less, and in all but one case negative smears were found thereafter For opinions on the virtue of different methods, varying lengths of fever sessions, prevention of reactions, and contraindications and so on, reference should be made to papers cited

Complications and Prognosis According to Lees,⁶ the prognosis in

cases of gonorrheal arthritis in which suppurative reactions are not present is "invariably good" as far as joints are concerned, particularly if roentgenograms show no destruction of articular surfaces and if proper treatment is instituted. Myositis is the commonest complication, being present in 80 per cent of the acute and all of the less chronic cases. Keratoderma blennorrhagicum was noted occasionally.

TUBERCULOUS ARTHRITIS

Tuberculous arthritis is characterized by pain, swelling, and stiffness of the affected joint or joints, increased local heat, and atrophy of surrounding tissues. Redness may or may not be present, in late stages it is usually absent. The condition is indolent, is characterized by remissions and exacerbations, and is usually progressively destructive unless the disease is checked by resting the joint in splints or by arthrodesis. The onset is usually gradual. A third to a half of the patients suffering therefrom present an associated visceral tuberculous lesion. Roentgenograms are not characteristic in early cases or in cases in which there is advanced destruction. In cases in which the disease is of moderate duration, roentgenograms are usually highly suggestive, atrophy, marginal erosion of bone, and interruption of the articular cortex being noted. Marked haziness of the joint and synovial thickening may be present. The joint space is usually well preserved until the late stages of the disease, because articular cartilage is peculiarly resistant to toxins of tuberculosis. An absolute diagnosis of tuberculous arthritis rests on the isolation by aspiration or biopsy of viable bacilli of tuberculosis in synovial fluid or membrane, as shown by inoculation of guinea-pigs and the demonstration of tuberculous tissue, that is, epithelial cells and lymphocytes in characteristic configuration with or without the presence of necrosis and foreign body giant-cells.

Roentgenographic Data. A tuberculous synovitis develops whether the primary focus of tuberculosis is in bone or synovia, and granulation tissue forms which tends to invade cartilage. Phemister and Hatcher⁷³ correlated the pathologic and roentgenographic findings. In some joints articular cartilages fit together accurately, while in others, particularly the knees, contours are different so that there are large areas of both free and contacted surfaces. In joints with both free and opposed surfaces of cartilage, the free portions are destroyed while the contacted areas are largely spared except at the margins. Subchondral granulations, free from tubercles, develop and aid in detaching the articular cartilage, which may persist for some time due to the absence of proteolytic ferments in the exudate. At this point roentgenograms show regional atrophy of bone, reduction of density of the bony articular cortex, and preservation of the normal width of the joint space. In joints like the knee, with areas of noncontacted cartilage, the articular cortex may be destroyed by surface granulations before any changes due to subchondral granulation may be detected in the articular

cortex of the opposed portions. Eventually, narrowing of the joint space is seen, the result of complete destruction of articular cartilage. In advanced stages, bilateral opposing sequestra are formed at the traumatized points of contact and weight bearing. These are shown in roentgenograms as relatively dense, conical shadows with incomplete lines of demarcation. Bony ankylosis almost never occurs, even when these secondary sequestra are present.

In adults, primary osseous tuberculosis is usually located in the epiphysis bordering the joint, although it sometimes extends into the articulation. The changes just described cannot be recognized in roentgenograms until atrophy and sequestration (usually unilateral) have set in. In children, owing to their relatively thick articular cartilages, destruction and detachment of the noncontacted portions are less complete. In swollen joints, with thinner cartilages and in older children, the pathologic and roentgenographic picture resembles more that seen for adults. Secondary invasion of bone at weight-bearing points produces extensive bilateral necrosis without sequestration.

The clinician, suspecting a tuberculous arthritis, places considerable reliance on the diagnostic abilities of his roentgenologist. Pomeranz⁷⁴ reminds us that, contrary to opinion, an early or positive roentgenologic diagnosis is no easy task. An accurate interpretation of this disease is extremely difficult, as criteria utilized in the roentgenologic diagnosis of tuberculosis are subject to diversified exceptions. The usual roentgenologic changes are synovitis and periauticular swelling, atrophy of bone or sclerosis, bone production and destruction in epiphysis and metaphysis, narrowing of joint space, sequestration, and the presence of cold abscesses or sinuses. In the genesis of tuberculous arthritis most or all of these changes are present. The roentgenogram is but a record of the disease at a given moment.

Synovitis, periauticular swelling, and atrophy of bone are common to all arthritides and are of limited value in the diagnosis of tuberculous arthritis. Atrophy of bone is usually marked, but its intensity is modified by numerous imponderable factors which complicate diagnosis. Sclerosis and bone production occur in tuberculosis even in the absence of a mixed infection. When sinuses exist, bone production may be absent. Diaphyseal tuberculosis in long tubular bones is rare, and roentgenologically the diagnosis is impossible. Wedge or cone shaped lesions are usually tuberculous. "Kissing" sequestra (occurring on both sides of the joints) are common in tuberculosis. Narrowing of a joint space which occurs late in an infection, despite associated destructive changes, is strong presumptive evidence of the existence of tuberculosis. Roentgenologically, the presence of a cold abscess specifically identifies the process as tuberculous.

Although tuberculous arthritis occurs most frequently in childhood and young adult life, it may affect the aged also, "senile sciofula" was the name given it by Sir James Paget. Dailing⁷⁵ felt that an arrested or active pul-

monary tuberculosis has the power in old age of instituting a tuberculous arthritis that runs a different clinical course from that seen in adolescence, and that such a senile tuberculosis is likely to be mistaken for hypertrophic osteo-arthritis. In early stages its differentiation from hypertrophic arthritis, he feels, may be possible. It begins with slight pain, stiffness, synovial swelling, and a limited effusion, and it may be associated with atrophy of muscle. Onset of suppuration furnishes an indication for exploration. The diagnosis is made on finding bacilli of tuberculosis in aspirated pus. The progress of the disease is more rapid and the process more destructive than in the young, but in spite of its greater severity in the aged the disease usually runs a less painful course. Darling reported two such cases—that of a man aged 66 years, with advanced pulmonary tuberculosis who had subacute swelling of a knee considered by the roentgenologist to be septic arthritis, and that of a man aged 83 years with an old, presumably inactive apical tuberculosis, who had involvement of an elbow. In both cases exploration revealed pus in which bacilli of tuberculosis were found.

Evaluating various aids to an early diagnosis of tuberculous arthritis, Cooperman⁷⁶ believed that biopsy and guinea-pig tests are the most reliable. The significance of the von Pirquet and Mantoux tests is lost with advancing years. Focal reactions with intracutaneous tuberculin are not specific, roentgenograms may suggest tuberculosis when another type is later proved to be present and may be long negative in tuberculous joints. An illustrative case was given—that of a boy 13 years old who developed monarticular arthritis of a knee. Six months later roentgenograms were still essentially negative. A roentgenogram of the chest showed infiltration of one upper lobe. The Mantoux test was positive. Examination of aspirated material by direct smear was negative but the guinea-pig test was positive for tuberculosis. Exploration of the knee confirmed the diagnosis.

Ordinarily, for reasons not well understood, tuberculous arthritis involves but one joint, in some cases, however, two or more joints may be involved. Nevertheless chronic monarthritis is so characteristic of tuberculosis that when a patient presents himself with such a condition, tuberculous arthritis is generally first considered, and when more than three joints are the seat of arthritis the probability of tuberculosis being the etiologic agent is considered remote. Ghormley and Brav,⁷⁷ in a series of 168 cases of tuberculous arthritis of the knee, noted involvement of two joints in 22 cases (13 per cent), of more than two joints in nine cases (5 per cent). Twenty of 24 cases of monarticular involvement thought to be tuberculous were later proved by A. D. Smith⁷⁸ to be otherwise. Joints involved were the knee in 18 cases, hip in four, elbow in one, and tarsus in one. The ages of the patients were 19 months to 35 years, averaging 14.5 years. The duration of symptoms (a few months to 10 years), and the involvement of only one joint, were suggestive of tuberculosis. The joints presented characteristics which have been considered classic for tuberculosis but which Smith

felt were just as common in non-tuberculous arthritis, that is, monarticular involvement with swelling but with little tenderness or heat, with limitation of motion from muscle spasm and atrophy of adjacent muscles. Roentgenograms suggested a diagnosis of tuberculosis in five cases, in others the findings were indefinite and variable, but so they may be even in proved tuberculous arthritis. The tuberculin test was positive in 9 cases, doubtfully positive in three, and negative in eight. Exploration of the joint was done in each instance, the objective appearance of joint tissue conformed to that seen in many cases of synovial tuberculosis: a moderate excess of clear, yellow synovial fluid, synovial proliferation, and pannus formation. The pathologic sections, however, did not show tuberculosis in any case, the picture varying from that of an acute to that of a chronic inflammatory process. Cultures of tissue were generally negative. Guinea-pig tests were done in 22 cases and were negative. This test, the author felt, was not very useful because the results cannot be learned for six weeks and it is inconclusive if negative.

Smith concluded that (1) cases of monarticular chronic arthritis are often not tuberculous but of a "nonspecific type," simulating tuberculous arthritis in many respects, (2) it is often impossible to differentiate these lesions from those of tuberculosis by physical or roentgenologic examination, (3) laboratory tests are often not helpful, although a repeatedly negative Mantoux test is suggestive, and (4) aspiration of joint fluid and the guinea-pig tests are not as useful as biopsy, which gives information immediately available and which is the only certain method of making the diagnosis. Even so, the gross appearance of the joint may suggest tuberculosis, but the pathologic sections show nontuberculous inflammatory changes.

"Tuberculous Rheumatism" This is an entity which has never received general recognition in this country but which has gained acceptance in Europe, particularly in France. Poncet, in 1897, described the condition under the term "rheumatisme tuberculeux." His views have been modified and extended somewhat by others. The term "tuberculous rheumatism," as used by its proponents, designates a form of polyarticular disease distinct from tuberculous arthritis yet also related to a tuberculous infection. Whereas in tuberculous arthritis viable bacilli of tuberculosis are found or presumed certainly to be present, in tuberculous rheumatism their presence in joints is not necessarily presupposed. The disease "tuberculous rheumatism" is thought to result from the action of diffusible toxins, an allergic reaction to bacilli of tuberculosis elsewhere, an ultravirus of tuberculosis, to attenuated bacilli, or to trophic changes coincident with tuberculosis elsewhere in the body. The clinical picture of "tuberculous rheumatism" is supposed to resemble in one case atrophic arthritis, in another hypertrophic arthritis, and in still another acute rheumatic fever so closely that it is clinically indistinguishable.

Ory⁷⁹ and Cooperman⁸⁰ favor the acceptance of such an entity, have renewed the arguments in its favor, and suggest that it is not uncommon

Copeiman studied four cases of atrophic polyarthritis believed by him to be "proved tuberculous polyarthritis" (i.e., tuberculous rheumatism), on clinical grounds alone they were indistinguishable from "infectious arthritis of known etiology" It is distinguishable from streptococcal arthritides, however, after a study of its evolution, clinical behavior, anatomic and pathologic structure, and roentgenographic alterations All four of his patients had pulmonary tuberculosis, in one case there were bacilli of tuberculosis in the sputum, in another a positive guinea-pig test Biopsy was done in all four cases In two of the cases, swelling and vacuolization of the intima of blood vessels, giant cells, necrosis, and endothelial cells were found the preponderance of endothelial cells and edematous infiltration being the characteristic feature In two other cases tissue from knee joints revealed "typical tuberculous pathologic changes" In some cases, however the articular lesions did not show the specific picture of giant cells and tubercles, the cytologic picture could not be distinguished from that of ordinary inflammation, and biopsy and guinea-pig inoculation were necessary to prove the relationship of tuberculosis

Ory was of the opinion that various species of tuberculous rheumatism are larval expressions of tuberculosis, arising in persons infected with but few bacteria, or with a weakened virus, or great bodily powers of resistance

(For a further appraisal of this condition the reader is referred to an article which has just appeared and which more properly belongs to our next review Brav and Hench Tuberculous rheumatism—a resume, Jr Bone and Joint Surg., 1934, xxii, 839-866—Ed.)

SYPHILITIC DISEASE OF JOINTS AND BURSÆ

Syphilitic disease of joints and contiguous structures has been reviewed by Kling⁸¹ and O'Reilly⁸² The literature would indicate that syphilitic arthritis can imitate every form of joint disease, and that it occurs in from 2 to 20 per cent of cases of syphilis In cases reported the condition has resembled acute febrile infectious arthritis, atrophic, or hypertrophic arthritis Monarticular and polyarticular forms are noted, from a simple effusion to gummatous granulation and finally to destructive processes with deformity and ankylosis Symptoms are usually less notable than pathologic findings Pain may be absent or slight and it is often nocturnal (O'Reilly) Congenital syphilitic diseases of joints are more common than acquired types and include osteochondritis, with secondary synovitis, simple synovitis single osteo-arthropathy, usually with night pain or gummatous affections of synovia Acquired syphilitic disease may be marked by frequent arthralgia, synovitis, and hydro-arthroses or gummatous arthritis, perhaps secondary to osteitis O'Reilly cited five representative cases, all with positive Wassermann reactions, and all clearing completely or markedly during specific treatment a case of painful feet, two of polyarthritis simulating atrophic arthritis and two of hydro-arthrosis The results of therapy help to verify the presumption of the syphilitic cause of the condition

In 112 cases of arthritis with effusion Kling discovered nine which he diagnosed as syphilitic seven of simple synovitis, one of synovitis and juxta-articular gumma, and one of synovitis with osteochondritis and periostitis. All occurred in the late stage of infection. The Wassermann reaction on joint fluid as well as blood was strongly positive in eight cases, weak in one. A search for syphilis should be made in cases of involvement of one or both knees, with only slight pain, muscle spasm, and periarticular thickening without systemic manifestations. Rigid technic is required to avoid false Wassermann reactions on joint fluid. Kling does not accept positive Wassermann reactions in joint fluid as conclusive proof of the nature of the disease, but a positive reaction in joint fluid with a negative reaction in blood is suggestive, and a negative reaction in joint fluid of a known syphilitic is by itself proof of the nonsyphilitic etiology of the arthritis. Therapeutic evidence is important and is based on the inefficiency of nonspecific, and a characteristically successful response to specific, therapy. Marked and prompt restoration of joint function may ensue, as occurred in the case of Keefer and Myers⁸³ in which there was subacute febrile polyarthritis, painful lymphadenopathy, and maculopapular syphilids.

Syphilitic Bursopathy Only 34 cases are recorded, according to Morrissey and Reynolds,⁸⁴ who discuss a case of ulcerating patellar bursitis associated with cutaneous syphilitic ulcers.

"Charcot Joints" This term refers to enlarged, relatively painless, hypermobile joints of neuropathic origin which occur most commonly in tabes dorsalis but also in syringomyelia. In recent reports its usual characteristics are reviewed. A case of syphilitic Charcot's disease of a hip continued to progress in spite of intensive specific and nonspecific treatment by Hunsaker.⁸⁵ Collapse of the fifth lumbar vertebra occurred in a tabetic patient seen by van Nostrand and Baillie.⁸⁶ Warfield⁸⁷ observed three patients with Charcot's disease of an elbow joint two with tabes and one with syringomyelia.

RARER TYPES OF SPECIFIC INFECTIOUS ARTHRITIS

Typhoid arthritis is reported as a complication in from 1 to 12 per cent of cases of typhoid fever. It may be polyarticular or monoarticular. Recovery of joint function or ankylosis may occur. Occasionally suppuration is produced. Typhoid arthritis occurred in two of 161 cases of typhoid fever seen by Keller.⁸⁸ Typhoid spondylitis is one of the less common varieties. A number of cases of spondylitis in which roentgenograms simulated "typhoid spine" were seen by Woldenberg⁸⁹ among veterans who had never had typhoid fever but who had received typhoid inoculations. No relationship could be proved, however. (The data are meager, but roentgenograms and descriptions suggest ordinary varieties of spondylitis — Ed.)

Arthritic complications are listed as occurring in certain exotic diseases

dengue, melitococcosis, undulant fever, Bang's disease, certain spirochetal infections such as sodoku and yaws, and leprosy (Labendzinski, 1931) In association with undulant (Malta) fever, Kulowski and Vinke⁹⁰ saw an instance of spondylitis and O'Donoghue⁹¹ one of septic arthritis of a hip In the first case low back pain began two months before the onset of fever Roentgenograms showed destruction of lower lumbar interarticular facets A large abscess was opened, yielding cultures of *Brucella melitensis*, bovine variety In the second case chills, fever, and pain in a hip appeared seven weeks after the onset of the initial fever The hip was drained and from thin pus specific organisms were cultured A solid ankylosis resulted Blood agglutinations were positive in both cases, 1:320 and 1:160

Haverhill Fever In 1926 an epidemic of acute febrile polyarthritis ("erythema arthriticum epidemicum"), associated with a rash, appeared in Haverhill, Massachusetts The clinical features, described by Place, Sutton and Willner (1926), included polyarthritis appearing on the first to fourth day of illness In some cases joints were only mildly attacked, in others marked swelling, redness, and hydrops appeared for 3 to 14 days A specific organism, "*Haverhillia multiformis*," was isolated from the blood (Parker and Hudson, 1926) An isolated case is described by Hazard and Goodkind⁹² The source of infection is unknown but may be from milk Specific agglutinins are present Crippling may be marked for a time but recovery of joint function tends to recur in one to two months (See also Place, E. H., and Sutton, L. E. *Arch. Int. Med.*, 1934, liv, 659-684)

"Madua Foot" This should not be classed as a form of arthritis, as all structures are involved, skin, soft tissues, joints and bones It is of interest to note, however, that acute, and later chronic, granulomatous arthritis developed in rabbits injected by Gammel and Moritz⁹³ with *Monosporium apiospermum*, establishing the pathogenicity of the fungus Synovia, cartilage, bone, and periarthicular soft tissues were involved Abscesses and granulomas developed

RHEUMATIC FEVER

Incidence Some (Poynton and Schlesinger, 1931) state that there has been considerably less rheumatic fever since the World War In New York the rate apparently was definitely declining between 1906 and 1919 (Lambert, 1920) Studying the yearly incidence in two New York hospitals, where 1,152 cases of rheumatic fever have been encountered since 1897, Davis⁹⁴ noted a decline from 1897 to 1919, a rise since 1919 Rheumatic fever follows a cycle in incidence and virulence similar to that found in many acute infectious diseases In rheumatic fever the cycles are of three to five years each

Since rheumatic fever and rheumatic endocarditis are usually not reportable diseases, we have no satisfactory mortality statistics, at least in the United States In England, 250,000 out of 5,000,000 school children suf-

fer from "rheumatism" (Clarke⁹⁰) Most European writers state that rheumatic fever is chiefly a disease of the poor, being 20 to 30 times more frequent among them than among those of the upper classes Since but few data are available regarding the social incidence of rheumatic fever in this country, Paul and Leddy⁹⁶ studied the incidence of rheumatic carditis at Yale University, examining health records of undergraduate and graduate students who attended the university between the years 1920 and 1930 Such a group represents a selected number of young men mostly from the northeastern part of the country and mostly from the upper economic strata The incidence of rheumatic heart disease among 7,914 undergraduates was found to be only 8.2 per 1,000, as compared with 15 per 1,000 the average figure obtained from statistics of comparable age groups (18 to 25 years) of the general male population in the same locality The incidence among the 4,455 graduate school students was 11.4, an incidence somewhat higher, possibly due to the fact that a smaller percentage of the graduate students came from homes of means Among undergraduates who had attended expensive boarding schools the incidence was only 5.8 per 1,000 as compared with 12.5 per 1,000 for those from high schools These studies thus support the contention that rheumatic fever is a disease that has a lower incidence among people of ample means From the control studies of Paul and Leddy, however, it appears that the factor of poverty does not have as important a predisposing role in determining the incidence of rheumatic fever or rheumatic carditis as it does in tuberculosis

Considering the question of economic status as a predisposing factor, Davis compared the curve of yearly incidence of rheumatic fever in a New York hospital population to the curve of retail commodity prices in the United States and was unable to conclude that fluctuations in economic welfare produced by "boom years" and depression had any influence on morbidity due to rheumatic fever Plotting the curve of incidence beside that of the annual rainfall in New York City, he concluded that wet weather was a definite factor in increasing its prevalence

Climatic conditions and geographic location are said to influence markedly the incidence of rheumatic fever McLean⁹⁷ believed that these factors influence the clinical manifestations of rheumatic fever more than the general incidence of the disease It seems to be more common and more severe in the colder parts of the temperate zones than in the warmer parts, and it is extremely uncommon in the tropics It is rare in Louisiana and Georgia and half as common in Virginia as in Massachusetts Longcope (1931) noted that rheumatic fever in Baltimore is not associated with the severe arthritic manifestations that he saw in New York However, in Baltimore it is characterized by rheumatic carditis of insidious onset and mild exacerbations, and is as relentless in its progress toward destructive carditis In Birmingham, McLean⁹⁸ noted a similar state of affairs, rheumatic fever there being a disease primarily of the heart, characterized by an insidious onset, with cardiac involvement out of proportion to the moderately

severe and relatively infrequent arthritic and choreic manifestations. Based on admissions to the Children's Hospital, the general incidence rate was 1.79 per cent, being 3.6 per cent at the age of five years. Girls were 14 per cent more susceptible than boys. Arthritis occurred in only 22 per cent of 122 cases. A diagnosis of carditis was made in 83.6 per cent of cases. In Birmingham the incidence of arthritis is 46 per cent less, of chorea 26 per cent less, of cardiac disease 4 per cent greater, than in New York City. The incidence of rheumatic carditis without a history of other clinical manifestations of rheumatic fever was 50 per cent greater in Birmingham than in New York, and children apparently developed rheumatic infection and its cardiac complications at an earlier age in Birmingham than in New York. (These statistical differences are striking and should be verified elsewhere. It has been felt that if one were to have rheumatic fever, it would be better to have it down South. It would appear that although there may be less rheumatic fever in the South than in the North, when one does have it geographic location may actually be detrimental. For rheumatic fever, in part deprived of its dramatic warning signals of acute arthritis, chronic muscle pain, or chorea, may in the South escape diagnosis and early treatment which it might have elsewhere. Thus the insidious progress of rheumatic carditis may be favored.—Ed.)

To evaluate hereditary or constitutional factors, Irvine-Jones⁹⁹ studied the incidence of rheumatic fever in 500 families in Toronto and St. Louis, including 800 rheumatic persons in immediate family circle. Nonrheumatic families were also studied. Thirty-two per cent of the rheumatic families both in Toronto and St. Louis showed multiple instances of rheumatism. When a member of a family exhibits the clinical manifestations of rheumatic fever, the chance of its appearing in other members of the family is practically doubled. It was more common in more distant relatives in rheumatic families than among those of nonrheumatic families. Studying a small group of 20 persons who were actually living in close contact, it was found that the disease occurred among about 25 per cent of the unrelated boarders and among 65 per cent of those who were related. It simultaneously affected both twins of two pairs of identical twins but only one of each of eight pairs of nonidentical twins. It was more common in families where the father was affected. It tended to occur among blonds and red-haired persons. The greater susceptibility of girls to the disease was found chiefly in families in which the father was rheumatic. H. C. Jamieson¹⁰⁰ noted the familial tendency of rheumatic fever to appear among cousins.

Course and Symptoms. Various terms have been proposed in place of "acute rheumatic fever," to withdraw emphasis from an acute or a febrile stage, from the arthritic or carditic phases alone, and to include under one designation the various connected manifestations of the rheumatic syndrome. H. C. Graham¹⁰¹ has proposed the term "rheumaticosis" to designate the process as a long-continued, low-grade, all pervading indolent toxæmia primarily responsible for the insidious prodromes as well as for the more

frank characteristics of the disease, that is, tonsillitis and pharyngitis, chorea, arthritis, nodules, and carditis. With similar intent, Coburn¹⁰² uses the term "the rheumatic state." Dally¹⁰³ favors Cheadle's (1889) term "the rheumatic series." Sigler¹⁰⁴ reviewed the chief features of rheumatic fever. While the heart is the organ most often and most seriously affected, no organ of the body may escape the essential lesions of this state, namely, the sub-miliary node or Aschoff body, a small round-cell infiltration about minute blood vessels, especially in the muscular, nervous and the osseous systems.

Depending on what tissue is most severely affected, rheumatic fever presents the following clinical forms: (1) cardiac, (2) arthritic, an uncommon spinal form sometimes being characterized by stiff neck and a positive Kernig sign, which with fever and leukocytosis may simulate meningitis, (3) muscular, which is the most frequent form, next to the arthritic, and of which "growing pains" and a mild fever, possibly with slight carditis, may be the signs, (4) nervous, with chorea and occasionally "cerebral rheumatism," (5) pseudosurgical, in which rheumatic fever may be ushered in with relatively acute but indefinite abdominal symptoms for which operation has been erroneously advised and in which the typical symptoms of rheumatic fever appear later, and (6) septicemic, characterized by unexplained fever, fleeting pains, malaise, headache, drowsiness, weakness and occasional rash, all lasting for some weeks or more and the nature of which may be clarified by the later appearance of nodes, otherwise unexplainable pleural exudates and partial response of symptoms to salicylates.

Natural Course of the Disease Untreated Many false deductions are made as to the efficacy of certain measures in cases of rheumatic fever because so few careful observations have been made on the natural course of the untreated disease. No specific treatment and no antipyretics were given to a group of 105 patients who were studied by Graef, Parent, Zitron and Wyckoff¹⁰⁵ over a period of two years. One such group was affected chiefly by polyarthritis, another by chorea, another by structural carditis. Forty-seven patients were followed to the point where there was cessation of activity, evidenced by normal temperature, pulse rate, and leukocyte count, freedom from such heart signs as gallop rhythm, prolonged P-R interval or other significant electrocardiographic signs and pericardial friction, freedom from evidence of pulmonic or pleural infection, from choreiform movements, and from subcutaneous nodules or rashes. Patients were dismissed when they were considered "normal" for 2 weeks after the last signs of activity. Striking spontaneous remissions in temperature and arthritis occurred. The severity and duration of the disease corresponded well with that of patients who were treated. Six patients who had previously had severe rheumatic carditis died. The remaining 41 patients enjoyed spontaneous cessation of the disease. Graef and his colleagues concluded that the worth of "specific therapy" (tonsillectomy, salicylates, etc.) has not been proved and that an evaluation of any further treatment must be based on a comparison with such a basic study as is here reported.

Recent clinical summaries and observations on rheumatic fever are those of Burnett,¹⁰⁶ Gray, Fendrick and Gowen,^{107, 108} Meakins¹⁰⁹ and Cecil^{110, 111} Two new series of cases are analyzed McLean^{97, 98} reviewed the early manifestations of the disease in 258 children Brooks and O'Regan¹¹² studied its onset in 700 residents of New York City of all ages Of McLean's patients 126 were girls, 132 boys In general, they were pale, high-strung, nervous, irritable children who were easily fatigued, had poor appetites, and who were either losing weight or were not gaining it as they should The onset of the disease was between the ages of two and five in 75 cases, five and seven in 86 cases, and after seven years in 97 cases Eighty per cent gave a history of repeated tonsillitis and 50 per cent had tonsillar infection Dental infection was present in 19 per cent of cases, sinusitis in about 8 per cent Joints were involved in 68 per cent, chorea was noted in 27 per cent, and paroxysmal abdominal pains were noted in 28 per cent Constant systolic murmurs were found in 78 per cent of cases Anemia and underweight were frequent Only three patients had nephritis, and one pyelitis The onset of the disease was between January and April in 58 per cent of the cases The incidence and severity of respiratory infections during the first five years of life were apparently no greater in rheumatic than in nonrheumatic children

In New York City the diagnosis of rheumatic fever should present no difficulties, as Brooks and O'Regan felt that its mode of onset is highly characteristic, with a very distinctive type of arthritis and almost invariably early cardiac involvement Of 700 patients, 443 were males and 257 females Fifty patients were in the first decade, 140 in the second, 210 in the third, 171 in the fourth, 88 in the fifth, 26 in the sixth, 9 in the seventh, and 6 in the eighth decade of life The most frequent prodromes were infections of the upper respiratory tract The tonsils were considered infected in 382 cases, the teeth in 238 and the sinuses in 33 Adenitis appeared early in 187 cases All patients had fever but only 65 had chills in the early stage, 622 had the characteristic migratory, acute polyarticular peri-arthritis Mon-arthritis was rare, when it occurs, rheumatic fever is not the likely diagnosis Various skin manifestations, considered allergic, were encountered in 42 cases Renal involvement was very rare Sixty-three had early evidence of pulmonary, bronchial, or pleural disease Cardiac involvement was exceedingly frequent, being noted early in 493 cases, eventually in 606 (The authors said "Sixty-two cases were complicated by certain or possible gonococcal infection The two forms of arthritis may unquestionably be associated in the same case" In view of the fact that gonorrheal arthritis is so frequently preceded by a stage of fleeting polyarthralgia, one might consider this statement critically and wonder if some of the cases thus noted were not in reality gonorrheal arthritis, not rheumatic fever—Ed)

Schwarz¹¹³ presented an unusual case of rheumatic fever, the patient being a child of 17 months A complete clinical and pathologic study of the first attack was given The attack proved fatal one month after the onset

The disease ran a fulminating course, presenting clinically only fever, tachycardia, and pain in one joint. Its true nature was not suspected. The main pathologic lesions were cardiac—infamed valves, coronary thrombosis, myocardial infarction, lesions in the auricles and in the pulmonary artery.

Laboratory Data. Sedimentation Rates, Blood Counts, Electrocardiograms. Data on other than routine laboratory tests will be discussed later under studies on etiology and pathogenesis.

Further evidence is given that changes in the sedimentation rate are almost parallel with the varied progress and clinical alterations of the disease (Payne,¹¹⁴ Bach and Hill,¹¹⁵ and Poynton¹¹⁶). The test distinguishes between a false improvement, due perhaps to salicylates, and one due to recession of the disease. It provides a numerical gauge to the patient's progress—good or bad. Its persistent failure to return to normal, when fever and joint pains subside, is highly suggestive of the continued presence of active pathologic changes, such as a cardiac lesion. It may aid in deciding whether bed rest can be terminated. The rate is, however, uninfluenced by the degree of cardiac injury from a quiescent lesion. Payne has modified the usual technic, utilizing 0.4 c.c. of blood from one stab of the finger as being more practical for children.

It has been shown that a study of frequently taken electrocardiograms demonstrates disturbances in a high percentage of cases of rheumatic fever (Cohn and Swift, 1924, Rothschild, Sachs, and Libman, 1927). Master and Jaffe,¹¹⁷ who made daily electrocardiographic studies in 63 cases, found definite evidence of myocardial involvement in 100 per cent of the cases. The changes found were increased auriculoventricular conduction time, auricular fibrillation or flutter, heart block, R-S-T abnormalities, T-wave inversions, and widening and notching or slurring of the Q-R-S group. Since patients with atrophic arthritis showed no such changes, electrocardiographic alterations in a given case would suggest rheumatic fever rather than acute atrophic arthritis.

Pathologic Studies and "Complications." *Specific Granuloma.* Cytologic studies of the characteristic cell of the rheumatic granuloma have been made by McEwen.¹¹⁸ At present much uncertainty exists as to the nature and origin of the large basophilic, and often multinucleated, cells of the Aschoff body, and as to whether they originate from muscle cells, endothelial cells, connective tissue cells, or wandering or fixed phagocytic cells. McEwen examined them with supravital stains, a method previously used successfully in identifying cells in the lesions of tuberculosis and syphilis. As cells of the Aschoff body and cells of the rheumatic granuloma are essentially identical, and as rheumatic nodules are easily available and more readily handled than Aschoff bodies, nodules were studied on the assumption that conclusions drawn from them would apply equally to Aschoff bodies. The importance of establishing the nature of these cells in the Aschoff body and in the rheumatic granuloma lies in the occurrence of somewhat similar nodules in other diseases, such as syphilis, yaws, acro-

dermatitis chronica atrophicans, scleroderma, and especially atrophic arthritis. Scrapings of subcutaneous nodules from 10 patients with rheumatic fever were examined, also control material from various sources. They showed a great predominance of certain cells almost devoid of phagocytic power and not characterized by the reactions with neutral red that distinguish monocytes, epithelioid cells, and clasmatoocytes. Hence they differ from the essential cells of the lesions of tuberculosis and experimental syphilis. These differences are probably of a functional and developmental, rather than of a genetic, nature. The cells probably arise from undifferentiated mesenchymal elements of loose connective tissue, although it is possible that endothelial cells take part in their formation in some instances.

Subcutaneous Nodules Subcutaneous nodules of rheumatic fever are closely related to, if not identical with, those found frequently in atrophic arthritis. They are highly characteristic of the two diseases, and suggest to Dawson¹¹⁹ that the two may represent different phases of the same fundamental pathologic process. Such evidence, however, is presumptive and by no means constitutes proof of an identical cause.

Lymph Nodes The presence of Aschoff bodies in hyperplastic nodules in the superior mediastinum (regional nodes that drain organs affected by the disease) seemed to Fraser¹²⁰ to provide further evidence that the virus can pass from infected tissue into the blood stream via lymph channels.

Hemorrhagic Changes In addition to the characteristic perivascular (Aschoff) lesions of rheumatic fever, Coburn¹⁰² considers another lesion to be of rheumatic origin, because, although it has no distinct histologic appearance, it develops simultaneously with specific lesions and occurs at the height of the disease's activity, the first two weeks of an attack. Examination of 100 patients who died from rheumatic fever demonstrated the usual lesions, but it also demonstrated innumerable hemorrhages scattered purpura in the peritoneal cavity, lungs, ovaries, suprarenal glands, spleen, kidneys, over the sigmoid, in the mesentery, in the tricuspid, mitral, or pulmonary valves, in the ventricular endocardium, and in the white matter of the brain. The lesions are hemorrhagic, capillaries are dilated. Edema, but no detectable alteration in blood vessels, is present. They probably result from alterations in vascular permeability, with diapedesis, injury to mesodermal tissues, and resulting inflammatory reaction. In one case they were associated with acute renal insufficiency, in others with mania, with cutaneous lesions, and with asphyxia from hemorrhagic solidification of the lungs. In three cases the hemorrhagic areas were probably responsible for acute abdominal symptoms, for which operation was done at the onset of the rheumatic fever.

Cardiac Alterations Coombs,¹²¹ reviewing rheumatic heart disease, stated that the myocardium and the mitral valve are involved in 100 per cent of cases of rheumatic fever, the pericardium in 60 per cent, aortic valve in 50 per cent, and tricuspid valve in 30 per cent. Appreciation of the enormous morbidity and mortality produced thereby is still growing (Cecil,¹¹⁹

Sloan¹²²) Forty per cent of all cases of heart disease, the cause of more deaths in the United States than any other condition, are of rheumatic origin (McLean) During the past 50 years deaths from heart disease in the United States have increased 42 per cent, whereas those from tuberculosis have declined 44 per cent (Burnett¹⁰⁶) In England, 1,500 deaths a year are due directly to rheumatic fever, more than 20,000 deaths a year are due to rheumatic carditis, and at any one time 140,000 people in England are suffering from rheumatic carditis (Clarke⁹) Coombs¹²³ noted that about 32 per cent of cases of heart disease in private practice were of rheumatic origin There was five times as much rheumatic heart disease among children in Bristol, England, as in surrounding rural areas

Usually the earliest clinical indications of valvular injury are, according to Coombs, muffled apical sounds, which probably denote edema of the mitral or aortic leaflets, and the gradual onset of murmurs The early signs of cardiac inflammation may be trivial and their existence doubtful, the impulse a little wider to the left than it should be, the first sound at the apex weak and impure Within a few days this grows into a true apical systolic murmur, and the second sound at the pulmonary area becomes louder In severe cases there may be pericardial friction, an aortic diastolic murmur, and electrocardiographic changes In about a fourth of cases these signs gradually recede after a few days, disappearing within a year under prolonged treatment

We cannot enter deeply into a discussion of rheumatic heart disease, a field adequately covered elsewhere Three studies will be mentioned In 5,215 consecutive necropsies, 474 cases of rheumatic heart disease (9.1 per cent) were found by Davis and Weiss¹²⁴ Rheumatic carditis was directly responsible for death in 35 per cent of these 474 cases, it was contributory in 8.6 per cent Malignant endocarditis was associated with rheumatic heart disease in 4.4 per cent of the cases In 229 cases deaths from rheumatic carditis were distributed widely from the second to the fifth decades of life, the largest number occurring in the fourth or fifth decades Forty of 47 persons who had subacute bacterial endocarditis superimposed on rheumatic heart disease died before the age of 50 In all of 19 cases with malignant endocarditis superimposed on rheumatic heart disease death occurred before the age of 40 Rheumatic heart disease is frequently present with cardiac signs and symptoms as late as the seventh decade of life

In a given case, a favorable prognosis may, according to Poynton,¹¹⁶ be entirely altered by renewed activity Mortality is higher among boys, varies in both sexes in different years, but is greater when carditis occurs before five years of age In children, 30 per cent die in the first attack If mitral stenosis occurs before the age of 12, the prognosis is bad The presence of fever is not important as a guide to the severity of carditis, but nodules are of serious import, they were present in 27 of 72 fatal cases

Observations over a period of 10 years have been made on 450 children with rheumatic heart disease by Stroud, Goldsmith, Polk and Thorp¹²⁵

The average age at onset of rheumatic fever was 7.3 years. Of 307 children for whom records were complete, 41 per cent are dead or totally disabled, 59 per cent are able to work or go to school. A familial incidence at least as high as that of tuberculosis seemed apparent, with Italians and Hebrews more susceptible than those of American or Irish parentage. Sixty-one per cent of 428 attacks of rheumatic fever occurred between December and May, the greatest number in March. The location or number of valves involved had less to do with prognosis than the virulence of the infection, resistance of the host, and number of reactivations.

De la Chapelle and Graef¹⁻⁶ reported a case of polyserositis (Pick's syndrome) with rheumatic valvular disease, unusual in that it occurred without adherent pericarditis. Polyserositis during the course of rheumatic fever is rare.

Pleurisy and Pneumonia Pulmonary manifestations arise insidiously but rather commonly in severe rheumatic fever. It has been recognized for 200 years that lungs and pleura may be attacked by the rheumatic virus (Gouley and Eiman¹²⁷, March 1927). Further data on incidence, and on chemical and pathologic characteristics of these pulmonary lesions, are presented (Gouley and Eiman,¹²⁷ Howard,¹⁻⁸ and Myers and Ferris¹²⁸).

The symptoms of "rheumatic pneumonia" are not spectacular, an initial chill does not announce the pulmonary invasion, and a cough may or may not be present. Its physical signs are more prominent, but they must be sought as they may last only a few days, and its consolidations are transient. Râles may be absent during the stage of consolidation (Howard). Gouley and Eiman described the pathologic changes in nine cases. Such lungs are grossly different from those affected by common pneumonia. The pulmonary lesions show histologic characteristics identical with those of rheumatic fever elsewhere: focal perivascular lesions, necrotic and proliferative areas of the Aschoff type, vascular injury, rupture of capillaries with liberation of fibrin, endothelial hyperplasia, and an interstitial perivascular exudate of large endothelial cells. In areas of necrosis, polymorphonuclear cells are scarce. The consolidated areas, of India-rubber consistence, are not atelectatic as has been stated.

Rheumatic pleurisy occurs in 2 to 20 per cent of cases of rheumatic fever and, next to carditis, is one of the most frequent complications of the disease. Its pathologic characteristics are described by Howard, and by Myers and Ferris. Ten of the 15 patients of Myers and his colleagues had pleural effusions, three had fibrinous pleurisy, two had bilateral hydrothorax. Clinical characteristics were sudden onset, dyspnea, mild cyanosis, pain and increased temperature. The fluid of rheumatic pleurisy was noted for its hemorrhagic nature and the readiness with which its formation took place. Salicylates did not alter the course of pleural or pulmonary lesions (Myers and Ferris).

Kidneys Contrary to the experience of some (McLean, Brooks and O'Regan) who say that renal lesions rarely occur in rheumatic fever, acute

ephritis is said to occur in from 10 to 20 per cent of cases according to others (Gray, Fendrick and Gowen) who say, however, that it does not lead to chronic glomerulonephritis. In view of these statements a report by Shambaugh,¹³⁰ on uremia in a case of rheumatic fever is of interest. A young man entered the hospital in a state of circulatory collapse and marked dehydration, neither pulse nor blood pressure could be felt for two days. Almost complete anuria was present, but examination of a few cubic centimeters of catheterized urine showed it to be normal. Blood urea rose to 19 mg per 100 c c. Recovery followed appropriate therapy. Shambaugh assumed that uremia occurred in the absence of nephritis, chiefly because of an anuria from hypotension.

In 22 per cent of cases of rheumatic endocarditis a diffuse glomerulitis was observed by Bell¹³¹, in 3 per cent an embolic type of glomerulitis was found, percentages much higher than previously reported. Baehr and Schiffrin¹³² found diffuse glomerulonephritis only three times (1.3 per cent) in 235 cases of rheumatic endocarditis at necropsy. Its rarity as a complication of rheumatic fever is in contrast with its frequent occurrence following various diseases of proved streptococcal origin. The appearance of nephritis justifies review of a case to make certain of the diagnosis. Baehr and Schiffrin believed its occurrence may indicate the bacteria-free stage of subacute bacterial endocarditis, Libman's verrucous endocarditis (nonrheumatic), or periarteritis nodosa rather than rheumatic fever.

Etiology and Pathogenesis The cause of rheumatic fever has not been determined. There are three general theories: (1) the infectious theory, (2) the endocrine theory, and (3) the metabolic or chemical theory. The majority favor one of the variants of the infectious theory, of which there are three: bacterial, parasitic and virus.

Bacterial Variant of the Infectious Theory The editors of this review approach with considerable trepidation the task of elucidating present conceptions regarding this variant. It is difficult to interpret studies which the workers often frankly admit they do not themselves fully understand. It is almost impossible to compare results of different workers because of differing technique. Furthermore, the nomenclature of bacteriology and immunology is none too well established. Nevertheless, it is important to be familiar with some of the details of this work even if one makes no claim to special bacteriologic knowledge.

To follow the bacteriologic studies on rheumatic fever (as well as on atrophic arthritis) it will be helpful to visualize the data in table 2 which summarize the further subvariants of the bacterial theory and the names of a few of the men identified therewith. No attempt has been made to approach completeness as far as names are concerned. In brief the three subvariants of the bacterial variant of the infectious theory are these: (1) Rheumatic fever is the result of bacterial infection, a bacterial dissemination to affected tissues by way of a bacteremia of varying degree and persistency, the blood stream becoming infected either from an acute or chronic focus

TABLE II

The Bacterial Variants of the Infectious Theory of Rheumatic Fever

An approximate outline of current opinion

(Many other names might be added, these are representative)

I Bacteremic variant, the idea of general and direct bacterial infection

(a) Group specific, with one species of organism

1 *Bacillus* Bertrand (1928)—Achalme's anaerobic bacillus2 Diplostreptococcus Poynton and Paine (1900)—"*Diplococcus rheumaticus*"3 *Streptococcus viridans* Cecil, Nicholls and Stainsby (1929)—"typical strain"

Gray, Fendrick, and Gowen (1932)

4 *Streptococcus hemolyticus*5 *Streptococcus nonhemolyticus* (indifferent)

(b) Not group specific, i.e., with more than one type of streptococcus (as far as hemolysis is concerned)

1 "Generally," *Streptococcus viridans* Rosenow (1913), Swift and Kinsella (1917)

Clawson (1925)

II Toxemic variant, the idea of "bacterial intoxication" (theory of toxemia without, necessarily, bacteremia)

(a) Group (and strain) specific

1 Nonhemolytic streptococcus Birkhaug (1927)—"non methemoglobin-former"

Small (1927)—"*Streptococcus cardio arthritis*"

(b) Not group specific

III Allergic variant, the idea of bacterial allergy (the response of tissues hypersensitive to bacteria, the onus being more on tissues than on the infecting germ)

(a) Group-specific

1 Hemolytic streptococci Coburn (1931), Coburn and Pauli (1932) Group-, but not necessarily strain-specific

(b) Not group specific

1 *Streptococcus viridans* and *nonhemolyticus* Zinsser (1928)

Swift et al. (1928-1931)

Birkhaug (1929)

2 Various streptococci Clawson (1930)—generally viridans

Schlesinger (1932)

This is the theory of "bacterial infection," the infection being from (a) one specific group and strain of organism, (b) organisms that are group, but not strain, specific,^{*} or (c) any one of a number of different organisms. For full proof, the bacteremic theory, of course, needs the finding of positive blood cultures, preferably of an individual type or strain of organism in a significantly high percentage, a proof which is, so far, by no means consistently provided. (2) The "bacterial toxemic theory" is that rheumatic fever is due to a bacterial toxemia and not to an actual bacteremia, the toxemia arising from a localized infection with a specific kind of organism or any one of a number of organisms. While positive blood cultures are not to be expected under this conception, the isolation of a specific and identifiable exotoxin is required. The presumed isolation of such a toxin-producer by Birkhaug and Small (1927) has not been confirmed further. (3) The theory of bacterial allergy is that rheumatic fever is due to an allergic reaction to bacteria, a tissue hypersensitivity to bacterial products either from organisms that are group, but not necessarily strain, specific or more likely, a number of different organisms or the nucleoprotein thereof. In this country, streptococci of one variety or another are incriminated almost exclusively, although recently the nucleoprotein of staphylococci has been suspected. Bacilli are thought to be the responsible agents by a few workers in Europe but are here almost totally disregarded.

The chief proponents of the bacteremic theory have been Poynton and Paine (1914), Rosenow (1914), Miller,¹³³ and Cecil, Nicholls and Stainsby (1929). The chief proponents of the theory of bacterial toxemia have been Birkhaug (1927) and Small (1927). The proponents of the theory of bacterial allergy have been Herry (1914), Faber (1915), Zinsser (1928), Swift and his colleagues (1928-1931), and more recently Coburn (1932), Collis (1932) and Schlesinger (1932). Some who previously supported the first or second theory have since switched to the third.

The basis of reasoning has been studies of throat cultures, blood cultures, cultures of joint tissue, lymph nodes or subcutaneous fibrous nodes, agglutination tests, skin tests, and studies on precipitins, antistreptolysins, and opsonins in blood of controls and of patients with rheumatic fever, and the experimental production of arthritis in animals (table 3).

* The different streptococci isolated are still, in general, classified under three headings (species or groups): *Streptococcus viridans* (alpha or "green" streptococci), *Streptococcus hemolyticus* (beta streptococci), and nonhemolytic streptococci (indifferent, or gamma streptococci). There are of course many different strains (types) of these three species or groups. For example, there are many different strains of hemolytic streptococci, that of scarlet fever, for example, may be different from that of erysipelas, and is presumably quite different from the strain of hemolytic streptococcus isolated in the type of pharyngitis such as that which precedes rheumatic fever. One speaks, furthermore, not only of different strains of hemolytic (or other types of) streptococci, but also of different strains of the hemolytic scarlet fever streptococci (or of different strains of gonococci) of varying virulency. When one uses the phrase "group-specific, but not strain-specific," in referring to the cause of a disease or to agglutination tests, one means that the cause of the disease or of agglutination is just one group of streptococcus (*Streptococcus viridans*, for example, and never hemolytic or nonhemolytic streptococci), but not necessarily just one specific strain, but any one of a number of strains of that group of streptococcus.

Infectious Theory of Rheumatic Fever
Basis of approval for bacterial subvariants
(The names are but representative)

| Test | Results |
|---|---|
| 1 Throat cultures | <p>(a) Characteristic</p> <p>(1) Group and strain specific Small (1927)—<i>Streptococcus cardio-arthritidis</i> Coburn (1931)—hemolytic streptococci Coburn (but not strain) specific Coburn and Pauli (1932) Collis et al (1932)</p> <p>(b) Not characteristic Hitchcock (1928), Nabarro and MacDonald (1929) Graham and Thomson (1932)</p> |
| 2 Blood cultures | <p>(a) Characteristic</p> <p>(1) Group and strain specific Small (1927)—<i>Streptococcus cardio-arthritidis</i> Birkhaug (1927)—indifferent streptococci Rosenow (1914)—<i>Streptococcus viridans</i> Clawson (1925)—generally <i>Streptococcus viridans</i> Cecil, Nicholls and Stainsby (1929) —<i>Streptococcus viridans</i> Dawson and Boots (1931)—<i>Streptococcus hemolyticus</i> Gray, Fendrick and Gowen (1931)</p> <p>(b) Not characteristic Swift and Kinsella (1917), Moon and Edwards (1917), Coburn (1931), Lichtman and Gross (1932), Collis et al (1932), Cooley (1932)</p> |
| 3 Joint cultures | <p>(a) Characteristic Generally <i>Streptococcus viridans</i> Cecil, Nicholls, and Stainsby (1929) (b) Not characteristic Numerous e g Dawson and Boots</p> |
| 4 Agglutination | <p>(a) Generally characteristic Small (1927)—Indifferent streptococci, Cecil, Nicholls and Stainsby (1929)—<i>Streptococcus viridans</i> (b) Generally not characteristic Clawson (1925), Clawson and Wetherby (1932), Coburn and Pauli (1932), Gray, Fendrick, and Gowen (1932)</p> |
| 5 Skin sensitivity | <p>(a) Characteristic</p> <p>(1) Group specific Indifferent streptococci, Birkhaug (1927), Kaiser (1928) <i>Streptococcus hemolyticus</i>, Collis et al (1932)</p> <p>(2) Not group specific <i>Streptococcus viridans</i> and indifferent streptococci, Swift, Derick and Hitchcock (1928), Birkhaug (1929)</p> <p>(b) Not characteristic Lazarus-Barlow (1928), Graham and Thomson (1932)</p> |
| 6 Precipitins | <p>(a) Present but not specific Coburn and Pauli (1932) (b) Present and essentially specific, some cross precipitation formation—Schlesinger and Signy (1933)</p> |
| 7 Anti-streptolysins | <p>Increased formation (hemolytic)—Coburn and Pauli (1932), Todd (1932) Generally high, Small (1927)</p> |
| 8 Opsonins | |
| 9 Experimental acute arthritis with Aschoff-like bodies | |

Many results considered positive, others considered not characteristic

Blood Cultures The chief previous studies are those of Poynton and Paine (1900), Rosenow (1913), Herry (1914), Swift and Kinsella (1917), Suranyi and Forro (1918), Clawson (1925), Small (1927), Birkhaug (1927), Cecil, Nicholls and Stainsby (1929) and Nye and Waxbaum (1930)

Streptococci, usually of the alpha (viridans) or alpha prime type, have been isolated in 71 per cent of 28 cases of rheumatic fever by Gray, Fendrick, and Gowen In two cases hemolytic streptococci were isolated early in the attack, and later cultures revealed *Streptococcus viridans* Considering these differences, these writers felt that cultural standards for the classification of streptococci and the variations of these organisms under different environmental conditions must be taken into consideration They favor bacteremia and tissue infection as being essential for the production of rheumatic fever, although allergy may play an important part in making joints susceptible The cultural method used was a modification of that of Cecil, Nicholls and Stainsby, whereby a growth was obtained in one to six days instead of 17 to 30 days, subcultures are avoided One hundred and thirty-two cultures in 105 pathologic control cases were negative except in 15 instances in which positive blood cultures were to be expected

Wilson and Edmond¹³⁴ obtained positive blood cultures for 46 per cent of 67 children with "acute rheumatic polyarthritis" and for about the same per cent of two control groups consisting of children who were ill of other than rheumatic fever and a group of healthy children About half of the organisms recovered were streptococci (viridans or indifferent), the others were pleomorphic bacilli Because the recovery of organisms from both the rheumatic and the control series was comparable, the presence of these organisms in blood cultures of rheumatic children would not seem to be of primary etiologic significance unless one postulates that tissues of the rheumatic child are particularly sensitive to the microorganisms presumably present in their blood The findings suggested to Wilson and Edmond that bacteria may gain access to the blood stream of healthy and of sick children and are filtered off in various organs where they are destroyed During illness this transient bacteremia may be increased

Callow¹³⁵ likewise found about the same type and number (53 per cent and 66 per cent) of positive blood cultures in two groups (1) of 174 patients with rheumatic fever and (2) of 58 persons with acute upper respiratory diseases A smaller percentage (34 per cent) of cultures from patients with miscellaneous diseases was positive Eight per cent of 39 normal individuals gave positive cultures The organisms isolated in the rheumatic group were *Streptococcus viridans*, nonhemolytic streptococci and pleomorphic bacilli Under controlled conditions it was possible to transform selected strains of pleomorphic bacilli into diplostreptococci of either the green or the hemolytic type, similar in morphologic, cultural, and biochemical properties to the diplostreptococci isolated from rheumatic and

nonrheumatic patients. A specific etiologic relationship between the isolated organisms and rheumatic fever was questioned.

Cooley,¹³⁶ using Clawson's and Cecil's methods, found no significant organisms in blood cultures of 25 children during initial attacks of rheumatic fever. The positive results of Cecil and of Clawson could not be confirmed. A diplostreptococcus similar to that of Poynton and Paine was isolated from blood and pleural effusion in a case of "acute fulminating rheumatic disease" seen by Whitaker¹³⁷ who therefore believed that one streptococcus, such as Small's *Streptococcus cardio-arthritidis*, cannot be the sole cause of rheumatic fever. (The patient, a child of three years, had chiefly meningitic symptoms with preterminal pericarditis, cardiac enlargement, and pleurisy. No characteristic polyarthritis is described and there are no postmortem records. The diagnosis of rheumatic fever may be correct but is not proved.—Ed.)

Scudder¹³⁸ isolated a higher type of bacterium in cultures of the blood of a young man who died after repeated attacks of rheumatic fever. It was morphologically similar to Streptothriceae, but was later considered related to Mycobacteriaceae. It was also considered a secondary invader but the direct cause of the terminal embolic features.

Agglutination Tests Clawson and Wetzelby¹³⁹ were unable to place their patients in such distinct groups as atrophic arthritis, rheumatic fever, and hypertrophic arthritis. They believed that rheumatic fever and atrophic arthritis are closely related clinically, bacteriologically, and immunologically, and that they are the result of an infection, generally with *Streptococcus viridans*, of tissues hypersensitive to such germs. To determine how close an etiologic relationship exists, with Hilbert and Hilleboe¹³⁹ they studied streptococcal agglutination in 66 cases in which children had rheumatic fever and in 300 cases of "chronic arthritis." As controls, the serums of 110 normal persons, 46 with scarlet fever, and 20 with glomerulonephritis, were tested. Two strains of streptococcus were used, a *Streptococcus viridans* from the blood of a patient with rheumatic fever, and a streptococcus, which generally produced methemoglobin, isolated from the blood of a person with chronic arthritis. With the rheumatic fever strain, agglutinative titers of the serums of patients with acute rheumatic fever were higher than normal, those of patients with chronic arthritis were not. With the strain from the patient with chronic arthritis, titers were higher than normal in chronic arthritis but especially in rheumatic fever. With both strains titers were decidedly higher than normal in serums of patients with scarlet fever and glomerulonephritis. In all tests, including the normal serums, the chronic arthritis strain was agglutinated in higher dilutions than the rheumatic fever strain, and was apparently more sensitive to agglutination. These findings suggest that rheumatic fever and chronic arthritis are both caused by streptococcal infection but that neither is produced by a specific strain.

Positive agglutination tests to four strains of hemolytic streptococci were found by Keefer, Myers and Oppel¹⁴⁰ in 26 per cent of cases of rheumatic

fever, 54.5 per cent of cases of atrophic arthritis, and 15 per cent of cases of hypertrophic arthritis. No evidence of strain specificity was found. Positive agglutination tests bore no relation to the sedimentation rate or to positive cutaneous reactions to the nucleoproteins of hemolytic streptococci. The agglutinations were of a different order from those described by Tillet and Abernethy¹⁴¹ for serums of patients acutely ill with various diseases. The exact relationship between streptococcal agglutination and tissue response in cases of rheumatic fever and atrophic arthritis remains undetermined.

According to Hitchcock and Swift,¹⁴² exudates of joints, pleura, and pericardium in both rheumatic and nonrheumatic patients possess agglutinating properties to certain hemolytic streptococci and staphylococci but not to nonhemolytic streptococci, in other words properties similar to those of serums of febrile patients as reported by Tillet and Abernethy. Such observations on exudates, therefore, do not necessarily have a bearing on the question of the etiology of rheumatic fever.

The observation that agglutination tests need bear no relationship to cutaneous tests of skin sensitivity is further borne out by the work of Schultz and Swift¹⁴³ on reactions of rabbits to streptococci. Bacterial hypersensitivity to whole streptococci seems to depend more on previously induced focal infection than on circulating antibodies.

Skin Tests and Throat Cultures. In the face of contradictory and varying evidence regarding the specificity, or lack of it, of organisms isolated in blood cultures and the agglutinating properties of the serums of affected patients, many have adopted the allergic theory as an omnibus, believing it helps to explain such conflicting findings. Until recently the idea was dominant that the tissues were allergic first to viridans alone, next to many strains of viridans and indifferent streptococci, and possibly also to nucleoprotein of some staphylococci. The hemolytic streptococcus is now regarded as the chief, if not the sole, offender. Coburn believes that rheumatic fever represents an allergic reaction in individuals sensitive to the nucleoprotein of hemolytic streptococci present in "epidemic" sore throats. In his cases, blood cultures were essentially negative although several hundred cultures were made and 21 different mediums used. As a sequel to his monograph (1931) he has published with Pauli^{144, 145, 146} further studies on the relationship of throat infections with hemolytic streptococci to initial and subsequent attacks of rheumatic fever. They feel that certain climates are more favorable to streptococcal infections of the upper respiratory tract. In the tropics, where hemolytic streptococci are unusual in throat flora, scarlet fever is unknown and rheumatic fever is rare. In New York City, however, following epidemics of hemolytic streptococcal pharyngitis, the incidence of rheumatic fever rises precipitously, but during seasons when such throat infections are rare, acute rheumatic fever is unusual. The incidence of rheumatic fever, they insist, bears a striking relationship to geographic and seasonal distribution of hemolytic streptococci. Poverty and unhygienic conditions favor

activity of hemolytic streptococcal throat infections and rheumatic fever, and children of the wealthy rarely have such germs in the throat. Certain patients with rheumatic fever were transplanted to the tropics, while there, hemolytic streptococci previously present were not found in throat cultures. As long as they remained in the tropics the disease remained quiescent. The patient with rheumatic fever who escapes respiratory disease in the North or in the South remains free of rheumatic symptoms.

The chain of events leading to an attack they conceive to be as follows: the appearance of hemolytic streptococci in the throat one to five weeks before the onset of the acute attack, an active throat infection, tonsillitis or nasopharyngitis, followed by about a 10 day quiescent period, then the attack. Details are given concerning immunologic reactions, agglutination, complement fixation and precipitin tests, and antistreptolysins. They suspect that an attack of rheumatic fever may represent the immunity mechanism of certain individuals for handling products of hemolytic streptococci, and that it may begin when the immune response is at its height. At the onset of each attack a rise in antistreptolysin titer of a patient's serum occurs. Hemolytic streptococci isolated were not of a single type but fell into six antigenic groups, the majority being strong toxin producers. About 70 per cent of the toxins were neutralized by a monovalent streptococcal antiserum. Coburn and Pauli concluded that the specificity of the rheumatic response depends not entirely on the character of the parasitic germs but is related to some individual mechanism of the rheumatic patient.

The studies of Collis^{147, 148} and his colleagues, Sheldon, Bradley and Coombs,^{149, 150} apparently confirm Coburn's findings and conclusions. They believe that the silent or incubation period after the throat infection lasts 7 to 24 days, that hemolytic streptococci can be isolated during the throat infection but tend to disappear rapidly toward the end of the quiescent period, and that they often cannot be found when the rheumatism appears. This explains the failure of many to find a causal organism in the later stages. Blood cultures were repeatedly negative in all stages of the disease. Throat cultures of patients in a rheumatic fever ward were studied throughout several epidemics of sore throat. Relapses in cases of rheumatic fever occurred only after infections with hemolytic streptococci and not following throat infections of other varieties. Skin tests were performed with a hemolytic streptococcal endotoxin and with Dick's streptococcal exotoxin. They gave fewer positive Dick reactions than do normals, but whereas only 20 per cent of controls reacted to the endotoxin, all of the rheumatic fever patients had positive reactions. Rheumatic fever is therefore a contagious disease to those sensitive to hemolytic streptococci, although not contagious in the ordinary sense as more than one factor is responsible for its development. The streptococcal throat infection is no doubt contagious in the epidemic sense, but is followed only by rheumatic fever in the patient who is probably allergic.

Keefe, Myers and Oppel¹⁴⁰ agree that patients with rheumatic fever or

with atrophic arthritis seem to be allergic to the nucleoprotein of hemolytic streptococci, 77 per cent of 40 patients with rheumatic fever and 70 per cent of 20 patients with atrophic arthritis had positive skin reactions thereto as compared with 44 per cent of 207 controls. There was no relation between positive skin tests and agglutination tests. Although such patients are skin sensitive and allergic to such streptococci, the exact relationship between such streptococci and rheumatic fever or atrophic arthritis is not proved, and such streptococci are not necessarily the cause of the diseases.

Culturing throats and making skin tests to hemolytic and green streptococci in cases of rheumatic fever and in a control group, Graham and Thomson,^{1,1} and Gibson, Thomson and Stewart^{1,2} found that there were no essential differences between either group in skin reactions, in the presence or absence of hemolytic streptococci in sore throats, or in the relation between skin reactions and throat cultures, nor did there seem to be a relation between these factors and the patients' clinical condition. They concluded that the allergic skin reaction may be the result of previous infection with hemolytic streptococci, that the intradermal test could not be considered of diagnostic or prognostic value in cases of rheumatic fever, and that while rheumatic fever is probably due to some infective agent that agent has not yet been defined, although its entry may be facilitated by infection with hemolytic streptococci.

Antihemolysins A method of determining the presence of an infection by hemolytic streptococci without a bacteriologic examination has been described^{1,3}, it is a titration for antistreptolysins in serum. Streptococcal hemolysins are species (group) specific, but not type (strain) specific. To investigate the supposed relation between rheumatic fever and infection by hemolytic streptococci, Todd titrated the serums of patients with rheumatic fever for antihemolysins. Rheumatic patients whose symptoms were quiescent usually had a low antihemolysin titer. Patients with symptoms of active rheumatic disease had a high titer. The titer of individual patients rises during an attack of acute rheumatic fever, falls during a period of quiescence, and rises again with recrudescence of rheumatic symptoms. However, variations in the intensity of rheumatic disease are not necessarily accompanied by corresponding variations in antihemolysin titer. Patients suffering from infections other than rheumatic fever, apparently due to hemolytic streptococci, also show increases in the titer of their serum, but such increases are not present in normal persons or persons with diseases not associated with hemolytic streptococci. Injections of typhoid vaccine do not cause an increase of antihemolysins. Todd concluded that such studies supply further evidence that rheumatic fever is preceded by a hemolytic streptococcal infection but that they do not support the allergic theory or that of direct intoxication.

Precipitin Reactions Coburn and Pauli noted that, at the appearance of the rheumatic attack, individuals develop precipitins to protein fractions of hemolytic streptococci. These precipitins are not entirely specific since

there is some cross reaction with antigens of chemically related organisms Schlesinger and Signy¹⁵¹ also found streptococcic precipitins in the blood of rheumatic patients, but none, or very few, in controls. Their formation is delayed for about 10 to 21 days from the onset of nasopharyngeal infection. Their appearance generally foreshadowed a minor or major relapse of acute rheumatic fever. The peak of precipitin formation coincides roughly with the onset of the relapse. Such formation is but one of manifold reactions that take place in the patients' defense mechanism during the silent period. It is suggested that if the throat infection does not pass unnoticed, prophylactic measures, such as concentrated aspirin therapy, may prevent or minimize the impending relapse. Such medicine seems to delay the formation of precipitins.

Incidence of Other Clinical Evidences of Allergy According to McLean¹⁵⁵ and Irvine-Jones,⁹⁹ the incidence of so-called allergic manifestations (eczema, urticaria, asthma, and hay fever) is no greater in rheumatic than in nonrheumatic children. McLean furthermore found no difference in incidence or severity of upper respiratory tract infections.

Experimental Arthritis Adherents of the allergic theory may gain support from the work of Magrassi.¹⁵⁶ Intravenous injections of arthrotropic streptococci in rabbits produced septic polyarthritis with destructive changes in joints and no articular or cardiac similarity to rheumatic fever. Intravenous injections into rabbits of serum of patients with rheumatic fever did not produce the histopathologic picture of rheumatic fever, but its intra-articular injection produced nodular proliferations and areas of hyaline-fibrinoid degeneration, none of which were produced by similar injections of serum from febrile patients without rheumatic fever. Arthrotropic strains of living streptococci were injected subcutaneously or intra-articularly. Although local nodular lesions were seen, the development of such systemic lesions did not occur for from 8 to 25 days. Thereafter, the intravenous injection of the same strain of heat-killed streptococci markedly accentuated the production of systemic and diffuse lesions corresponding to those in rheumatic fever of man.

Summarizing data on the infectious theory leads to the obvious conclusion that our knowledge of the bacteriology and immunology of rheumatic fever is still inadequate, that the cause of the disease, which is not yet established, must await much further investigation. Differences of opinion, which now seem insurmountable, may disappear when more data are at hand, particularly regarding the extent to which transmutation of organisms may occur. Rosenow, for example, has long contended that one should not depend on bacterial grouping of streptococci on the basis of hemolysis, and that under changing environment a green streptococcus will readily assume properties of a hemolytic or indifferent type. He feels that, regardless of its hemolysing properties at the moment, the streptococcus probably responsible for each of the diseases, rheumatic fever and atrophic arthritis, is antigenically—serologically—or toxin-specific, acting both through endo-

toxins and exotoxins, especially the former. In little of the work here reviewed have investigators been convinced even of group-specificity, much less of strain-specificity. While they have "generally" found this or that germ, or this or that immune reaction, sufficient cross infection has been found to make it difficult to place them categorically in just one bracket of the schema in table 2.

Other Ideas on Etiology, the Rat-Flea Hypothesis. The theory was recently advanced by Clarke¹⁵⁷ that rheumatic fever is not due to streptococci, but to some protozoon or spirochete carried by the rat-flea (*Ceratophyllus fasciatus*). It is noted that rheumatic fever does not occur in the tropics, or particularly in the Malay states where the climate is inimical to rat-flea. Seasonal and geographic data were presented to strengthen the relationship. Clarke has presented statistics of others to show that, contrary to Coburn's¹⁰² report, hemolytic streptococci can be found in the tropics. It is suggested, however, that climatic conditions there do not favor complete maturation. Studying the incidence of various hemolytic streptococci in the tropics, he noted the fact that streptococci supposed to be the cause of scarlet fever are present in the Malay Archipelago, but the disease does not occur there. If hemolytic streptococci, considered causative of scarlet and rheumatic fever, are found in the tropics but their respective diseases are not, the difference in incidence of the disease in the tropics and elsewhere probably is not due to a difference of bacteria but lies in an agent, such as insect carriers, which can live in one climate and not in another. An infection by hemolytic streptococci may be an excitator of rheumatic fever, but its real cause is an as yet unrecognized organism (lying between bacteria and protozoa), possibly borne by the rat-flea.

Endocrine Theory. Stressing the importance of underlying rheumatic diathesis and criticizing the infectious theory for its inadequacies, Llewellyn^{158, 159} has stated his belief that the primary morbid process in acute rheumatism and chorea is one of endocrine-autonomic imbalance, involving especially the sympathetic divisions with their correlated endocrines, the thyroid and suprarenals (sympathetic) and the parathyroids (parasympathetic). Transient phases of thyro-adrenal toxicosis, affecting the cardio-respiratory or vasomotor system, are responsible for transitory cardiac arrhythmias which are a part of the clinical syndrome of acute rheumatism and chorea. If such a toxicosis is prolonged, as in recurring attacks of acute rheumatism or chorea, endocarditis and myocarditis result. Jones¹⁶⁰ discussed Llewellyn's^{161, 162} ideas further, and advocated ultra-violet irradiation in the prodromal stages of atrophic arthritis and for the prevention and treatment of rheumatic carditis on the assumption that ultra-violet light is required for the mobilization of tyrosine and cystine from the epidermis via lymph channels into blood. This mobilization is held to be necessary for the production of the hormones thyroxin, epinephrine, and insulin. It is further stated that if ultra-violet irradiation alone can mobilize tyrosine, it would go far to explain why rheumatism is most prevalent in the smoke-ridden areas.

where there is an inadequacy of sunshine Dally¹⁶³ also believes that the rheumatic diathesis is in reality an error of metabolism, which is "internally interwoven with hormonal disequilibrium, chiefly in the direction of imbalance of the sympathetic division of the autonomic endocrine system" Studies on acid-base balance, phosphate-sulphate excretion in urine, and calcium excretion in urine and feces are mentioned to illustrate the clinical changes considered characteristic of the diathesis Dally¹⁶⁴ stated that all children with murmurs or cardiac enlargement had a decreased alkaline reserve in the blood, and that their urine deviated from the acid-base balance in the direction of increased acidity Errors of purin and mineral metabolism were also suspected The hemolytic streptococcus is considered provocative of rheumatic fever only among persons who have such an altered metabolism

Treatment, Salicylates It has been claimed that salicylates in adequate doses reduce fever, relieve articular pain, shorten both the acute process and the hospital stay necessary, and help to prevent cardiac complications As to the analgesic and antipyretic values of salicylates there is almost complete agreement, but many do not agree as to their other virtues

It has been stated that there is no rationale for the administration of salicylates other than by mouth Brooks¹⁶⁵ felt that the most constantly effective avenue of administration is by rectum, whereby doses of 120 to 180 grains of sodium salicylate, in from two to four ounces of warm water or milk, are given one to three times a day through catheter and syringe (introduced six to eight inches up from the anus) Brooks considers salicylates of "tremendous value," giving more relief from agonizing pain "than all other measures put together" However, the administration of sodium salicylate does not prevent complications, shorten the course, or modify the prognosis It has nothing to do, Brooks felt, with the production of the severe anemia which often accompanies rheumatic fever, nor does it have any effect on anemia once it is present It has few unfavorable effects and does not disturb the heart When given properly, it is entirely without danger

Master and Romanof¹⁶⁶ studied the course of the disease in 30 cases of rheumatic fever in which patients were not given salicylates and in 33 cases in each of which they had 8 to 12 gm (120 to 180 grains) of salicylates daily One hundred per cent in each group developed heart involvement on the basis of electrocardiographic alterations whose qualitative and quantitative changes were essentially the same The course of the disease and the appearance of pericarditis and other complications were about equal in both groups There was no material shortening of the stay in the hospital Master and Romanof concluded that whereas at present salicylates are most efficient antipyretics and analgesics, they do not prevent cardiac complications or have a curative effect

A somewhat similar study was made by Perry¹⁶⁷ who gave 10 grams of acetylsalicylic acid, three times daily for 12 months, to each of 41 children

who were suffering from rheumatic heart disease. A control group was untreated. In the treated group relapses of a rheumatic nature (chorea, arthritis, or carditis) occurred in 12 per cent of cases, and in the control group in 18 per cent the difference being due, Perry felt, to factors other than the drug. No significant changes were noted in cardiac signs or general health, and little evidence was obtained that the prolonged administration of salicylates prevents relapses.

Poynton¹¹⁶ was disappointed in salicylate therapy for rheumatic heart disease, and believes that it may actually do harm. He prefers neocinchophen. According to Foxe¹¹⁸ the toxic effect is minimal when salicylates are combined with sodium bicarbonate or magnesium oxide. Salicylates are effective in smaller doses with magnesium oxide. He felt that 90 grains of sodium salicylate daily with 60 grains of magnesium oxide are the equivalent of 150 grains each of sodium salicylate and sodium bicarbonate combined.

Other Drugs. Magnesium also "potentiates" cinchophen, according to Tolstoi and Corke¹⁶⁹ who combined magnesium oxide and magnesium cinchophen into a preparation "magnephen" for the treatment of seven patients with rheumatic fever. Because of "magnesium potentiation," the therapeutic doses are smaller and nontoxic. Doses as large as 2,130 grains (142 gm.) over 26 days were well tolerated. The preparation relieves pain and reduces fever but has no influence on the rheumatic virus, as is evidenced by a persisting leukocytosis and increased sedimentation time.

The sodium salt of phenyl-ethyl hydantoin (nirvanol) was recently introduced in Germany and England for the treatment of chorea, acute and subacute rheumatism. The type of reaction it produces (drowsiness, stupor, fever, rash, eosinophilia, leukopenia), the results of its administration, its mode of action, and its dangers, have been reviewed (Poynton and Schlesinger, 1931, and Council on Pharmacy and Chemistry,¹⁷⁰ 1932). Schlesinger^{170a} has reported its presumably beneficial effects in the case of a seven year old boy who suffered for two years with chorea, rheumatic fever, and carditis. The drug stops chorea, reduces fever, and causes rheumatic nodules to disappear in some cases. In the discussion of this report the use of nirvanol was sharply criticized by Slot,¹⁷¹ Collis,¹⁴⁸ and Findlay,¹⁷² who not only consider it useless but sometimes quite dangerous. Schlesinger insisted that it is only dangerous if given in the wrong type of case, such as in chorea or rheumatic fever where mental symptoms are a dominant factor. No reports of its use in rheumatic fever have appeared in American literature although it has been used for chorea. Satisfactory results in chorea were obtained in 15 cases by Murray-Lyon,¹⁷³ in 72 cases by Dennett and Wetchler,¹⁷⁴ in 16 cases by Whitaker¹⁷⁵ and in 21 additional cases by Dennett.¹⁷⁶ No relief was noted in three cases by Jones and Jacobs,¹⁷⁷ who observed a dangerous pulmonary hemorrhage in one, or in six cases by Weinfeld and Cohen.¹⁷⁸ Facial edema was noted in one case (Murray-Lyon). Nirvanol has not been accepted by the Council on Pharmacy and Chemistry¹⁷⁰ because, although a fairly large percentage of patients with

chorea are relieved thereby, side actions are disagreeable, sometimes dangerous, and the treatment is too severe to justify its use except in very resistant cases

Tonsillectomy There are still considerable differences of opinion as to the value of tonsillectomy in the treatment and prophylaxis of rheumatic fever and carditis Collis, Bradley, and Coombs¹⁴⁹ feel that tonsillectomy in the prevention of rheumatism is a lost cause Many of McLean's patients made little or no improvement after the tonsils and adenoids were removed, but in those cases where the results of tonsillectomy were disappointing, an infection in the sinuses was almost invariably found later

Considering the fact that removal of foci, particularly tonsillectomy, has been carried out strenuously in the past 25 years, Davis⁹⁴ agreed with others that removal of foci has not influenced the clinical course or spread of rheumatic fever Of 185 patients with rheumatic fever, 88 per cent had their tonsils removed but 77 per cent had recurrences within one to eleven years (Ingerman and Wilson, 1924) Of 97 patients who did not have their tonsils removed, 80 per cent had recurrences Davis recounts Kaiser's statistics (1930) Rheumatism occurred among 8 per cent of 20,000 school children who had had their tonsils out at least five years previously It occurred among 10 per cent of 28,000 children who still had their tonsils Recurrences of rheumatic fever, however, were decidedly less common and the incidence of carditis and chorea seemed less in the former group

When rheumatic heart disease is present in children, tonsillectomy is a serious step, according to Poynton, and should be done preferably in a period of quiescence Herrick¹⁷⁹ also believes that tonsillectomy during an acute attack of rheumatic fever may be dangerous, after tonsillectomy, the blood culture may become positive and the clinical picture may change for the worse In general, it seems best to wait until the acute manifestations have subsided However, in the prolonged and recurrent cases, Herrick believes a different attitude may be taken with advantage

Tonsillectomy during an acute attack of rheumatic fever is considered by Robey¹⁸⁰ to be not only essentially harmless, but often of distinct value, and in his experience has sometimes proved an efficient means of stopping an attack when ordinary measures failed Cases are described in which fever and arthritis persisted beyond the usual period in spite of intensive medical treatment and in which within a few days after tonsillectomy symptoms disappeared In two or three cases only temporary recrudescences of joint symptoms followed tonsillectomy during fever, but they promptly disappeared Tonsillectomy in the presence of fever and inflamed joints is no more dangerous than tonsillectomy in the interval between attacks It should not be performed while acute tonsillitis is present, but this question seldom arises since acute rheumatic fever is usually a sequel, not a concomitant, of tonsillitis Only complete enucleation is successful, radium and roentgen-ray treatments to tonsils are inadequate

Stroud and his colleagues¹² concluded that though there is no positive

proof that routine tonsillectomy prevents primary or subsequent attacks of rheumatic fever, such a procedure, if combined with careful examination of the sinuses for infection, is still justified Cecil¹¹⁰ also advocated giving the patient the benefit of the doubt, and he advises tonsillectomy, as also does Miller¹⁸¹

Although Robey was of the opinion that tonsillectomy during the acute attack is not essentially dangerous, and in individual cases may be of benefit in shortening attacks, he, with Finland and Heimann,¹⁸² believed that a study of groups indicates that tonsillectomy has little influence on frequency of recurrences Six hundred and fifty-four consecutive patients were admitted to a hospital on account of "acute migratory polyarthritis" Many had undergone tonsillectomy previously, in some cases the tonsils were removed while the patients were in the hospital Those whose tonsils had been removed previously had on the whole a similar course in the hospital to those operated on after admission The latter, however, had a slightly longer period of joint symptoms and of hospitalization than those whose tonsils were left untouched

Vaccines, Antigens, Serums Their opinions on the value of the newer bacterial products in the immunization and desensitization treatment of rheumatic fever have not been re-stated during the past two years by the originators Whitten¹⁸³ has reported on the use of Small's *Streptococcus cardio-arthritidis* (S C A) bovine serum intramuscularly, and S C A antigen given later subcutaneously In the author's limited experience acute rheumatic fever responded promptly to the antiserum In every case (number not stated) the injection of 20 c c of antiserum was followed by disappearance of fever and arthritis within 24 hours, the patient to all outward appearances being cured Three of the author's local colleagues reported similar results Recalling reports of failure by others, Whitten believes Small's products are now in a greater state of perfection Five patients with chronic rheumatic endocarditis were definitely benefited Each time antiserum and antigen were given, signs and symptoms of cardiac decompensation diminished Small (1927) and others originally had difficulty in planning dosages which would avoid reactions The author's plan is detailed

Collis and Sheldon¹⁸⁰ treated 47 children who had rheumatic fever with intravenous injections of a vaccine of heat-killed hemolytic streptococci In some cases the treatment was discontinued for various reasons, such as the development of an acute sore throat or the appearance of a pericardial rub The treatment had no effect on vague pains in limbs loosely termed "sub-acute rheumatism" In acute cases, when the treatment was well borne, "encouraging clinical improvement" was noted skin tests became negative in 64 per cent of cases and agglutinins appeared at times in the blood serum Streptococcal vaccine given intravenously to 10 patients with rheumatic cardiovascular disease, by Stroud, Bromer and Gallagher,¹⁸⁴ did not diminish the incidence of acute exacerbations of rheumatic fever the following season

Results were comparable to those observed for 10 untreated controls and for 10 who were given typhoid vaccine intravenously. Three or four in each group obtained some immediate relief, however.

Wilson and Swift (1931) observed that 45 per cent of children with rheumatic fever who were treated with hemolytic streptococcal vaccine remained free of rheumatic arthritis for from 16 to 24 months, compared to 18 per cent for those not so treated. The result may have been merely coincidental or from immunization or desensitization. Further observations in this group of 166 cases and in an additional 141 cases have been made by Wilson, Joseph, and Lang.¹⁸⁵ Vaccine was stopped in some cases and continued in others, using variously typhoid bacilli, *Streptococcus viridans*, or hemolytic streptococci intravenously. The results indicated that intravenous vaccination with various antigens in the doses used did not influence the incidence of recurrence of rheumatic activity, and that the temporary diminished incidence of recurrence previously noted after intravenous treatment was probably unrelated to the treatment.

Additional Treatment A review of six years' experience with the treatment by roentgen irradiation of 32 patients with rheumatic heart disease is given by Levy and Golden.¹⁸⁶ Seven of the 32 have since died. In eight cases there was no, or doubtful, improvement. Seventeen patients showed improvement, there was relief of paroxysmal cardiac pain with some, and improvement in the electrocardiogram with a number of them. (The report cannot be evaluated as no control series was studied—Ed.)

Whether a woman with rheumatic fever should subsequently be permitted to marry and have children is discussed by Meakins,¹⁰⁰ who was of the opinion that the guiding principle should be this: if a number of years without recurrence have elapsed since the original infection, if cardiac signs have been stationary, if there is no enlargement of the liver or engorgement of the lungs, and if the woman is able to do what an ordinary person can do, she should be permitted to marry but her husband should be told of her condition. Usually, patients take these matters into their own hands, and if they do not feel well they will not have children. A woman with mitral stenosis, without incapacity, has been known to have 12 children or more without trouble. If there are signs of failing circulation, the patient should not marry, she may go through one or more pregnancies quite well, but difficulties may develop later.

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EDITORIAL

BLOOD FROM THE DEAD FOR TRANSFUSIONS

ONE of the most perplexing problems to hospitals and to the medical profession is the difficulty of securing blood for transfusions in sufficient quantities at all times and at a cost within the reach of people of limited means who need it

Under existing conditions the procedure of transfusion is available for use only when the patient is able to pay for a donor, or when a voluntary donor is available, or when the cost can be met from charitable funds. Not infrequently none of these avenues are open and a patient urgently needing transfusion must do without.

To meet this situation scientists in Russia have for some years been studying experimentally in dogs the effects of transfusions in which the blood employed was obtained from a dead canine donor. In 1928 Professor Chaumov of Kharkov reported most favorable results in a considerable number of such canine transfusions.

The experiments were continued at the Moscow Institute of Hematology which has facilities and personnel for clinical, biological, surgical and biochemical procedures, and a laboratory for the manufacture and standardization of serum preparations. Here postgraduate courses are conducted in hematology and noteworthy studies have been conducted since the foundation of the Institute in the anemias, the treatment of various intoxications by transfusion, the perfection of transfusion apparatus and numerous other hematological problems.

It occurred to Professor Sergius Judin, chief surgeon of the Sklifasovski Emergency Hospital in Moscow, after studying the results at Kharkov, that blood from cadavers, if properly tested and aseptically handled, could be utilized for the living, and, since it was impossible for the Institute of Hematology to furnish from living donors the immense quantities of blood required at the Sklifasovski Hospital, Professor Judin collaborated with the Institute in a study of the use of blood from cadavers.

About two years after Professor Chaumov's reports on canine transfusions and after the Hematological Institute had concluded that human experimentation was justifiable, the first use was made of the blood from a cadaver for human transfusion. Under the direction of Professor Judin an engineer brought to the hospital in an exsanguinated, moribund condition due to a self-inflicted wound was transfused with blood from a human cadaver. This case was successful and after repeating the procedure on a series of cases Professor Judin reported the methods used to the Congress of Surgeons of the Ukraine at Kharkov late in 1930. Because of the existence of a statute which prohibited the removal of blood for embalming purposes prior to the completion of an autopsy, it became necessary to gain the ap-

proval of the Surgical Congress to legalize the procedure and so, at this meeting, a resolution was passed certifying to the scientific basis of the procedure, since which time the scope of Professor Judin's actions has been greatly extended and his methods are being used in many other large hospitals in the Soviet Union

For the recovery of blood from the dead there has been set aside a special pavilion at the Sklifasovski Hospital under the immediate direction of a woman assistant, Dr Skoundina. This pavilion consists of a number of separate rooms where cadavers are prepared in the same way as for a surgical operation, and an operating room where the cadaver is placed on a table at an inclined plane with a cannula in the jugular vein. The blood is collected in aseptic jars in which there is a solution of sodium citrate, a specimen is sent to the laboratory for a Wassermann and Kahn test, and for culture and typing, the jar of blood, properly identified, is then placed in a refrigerator awaiting the laboratory report on the blood and the report of the pathologist on an autopsy which immediately follows.

If the reports are favorable the type is recorded on the label and the blood is then available for use when needed, it being necessary only to warm it in a water bath to 104° F before transfusion. If either the laboratory or the autopsy reports indicate any deviation from the normal of the blood or the organs of the body the blood is immediately removed from the refrigerator and discarded.

As a result of a rather extended experience Professor Judin has reached some definite conclusions concerning the procedure which are of universal interest. He prefers the blood obtained from suicides, from those dying of heart disease or from traumatism. In the case of sudden death the blood retains its fluidity longer in the veins and it has been found that in such cases the blood will flow out by gravity after as long as twelve hours. Blood can be preserved without risk for any time up to about twenty-eight days and possibly longer, but Professor Judin prefers blood that is not more than twelve days old, in the belief that as age increases, its potency is affected. There is no preference as to the age or sex of the deceased and blood from an aged individual has given as good results as that from a young athlete. The blood is delivered to the patient by means of gravity through rubber tubing from a heated glass funnel elevated about three feet above the operating table.

The very extensive records available at the Sklifasovski Hospital of over 400 transfusions of the citrated blood from cadavers compared with an equal number of previous transfusions with whole blood lead Professor Judin¹ to the following conclusions:

(a) The new method assures an immediate supply of carefully typed, tested and cultured blood from human bodies which have been autopsied and found free from organic disease.

¹ JUDIN, SERGIUS. *La transfusion du sang de cadavre à l'homme*, Paris, 1933.

(*b*) There are fewer unfavorable reactions from the refrigerated supply than from the blood of living donors

(*c*) Because a sufficient supply of blood is always available at little cost, there need be no hesitancy in resorting to transfusion whenever indicated and a considerable number of lives has been saved, not to mention the more rapid convalescence of many grave surgical cases

(*d*) Transfusion is placed within the reach of all of the people and while the extraction and storage of blood from cadavers can only be conducted by large institutions, the blood can be transported by airplane or otherwise under proper conditions to any distant point and in any quantity

WILLIAM H. WALSH

REVIEWS

The Practitioner's Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M A (Yale), M D, F A C P David P Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital *Volume VII Pediatrics* Associate Editor DANIEL C DARROW, B A, M D, Assistant Professor of Pediatrics, Yale University Medical School XXXVI + 1211 pages, 92 illustrations D Appleton-Century Company, New York 1935 Price, \$10 00 a volume

The preceding six volumes of *The Practitioner's Library of Medicine and Surgery*, presenting respectively Anatomy and Physiology as Applied to Practical Medicine, The Technic of Physical and Laboratory Examination in Clinical Medicine, Practice of Medicine, Nontraumatic Surgery, Traumatic Surgery and Gynecology and Obstetrics, have been reviewed in THE ANNALS as they have appeared When complete the Library will total 12 subject volumes and a combined Supplement-Index

To Volume VII, *Pediatrics*, there are 34 contributors who have been chosen because of their knowledge and comprehension of the problems of the general practitioner in the field of the diseases of infancy and childhood The choice of chapter headings and the proportion of space allotted to each topic give further evidence of thoughtful regard for the needs of that large group for whom this work is planned As has been mentioned in reviewing the preceding volumes, the unusual, rare or controversial condition cannot be treated in an exhaustive manner in such a book Rather must the emphasis be placed upon those groups of affections with the prevention and treatment of which troublesome questions frequently arise Thus among the thirty-four chapters we find special attention is given to defective nutrition, diseases of the gastrointestinal tract, and the infections of childhood The chapters on diarrheal diseases of infants, diseases of the upper respiratory tract, pneumonia and tuberculosis are especially to be commended Less serious affections of frequent occurrence also are well treated as, for instance, enuresis, which is discussed in six pages abounding in good common sense Much less satisfactory is the discussion of diseases of the thymus which gives but slight implication of the constitutional significance of thymic hyperplasia In this connection it should be noted that 'thymus' can be found in the index only under 'gland' The final index volume will doubtless include a more comprehensive listing In style and execution this volume maintains the high standards of the series It will prove a very useful addition to the library of the practitioner

C V W

Human Personality and the Environment By C MACFIE CAMPBELL, M D 252 pages, 15 X 22 cm Macmillan Co, New York 1934 Price, \$3 00

"This book presents the substance of six lectures delivered before a lay audience at the Lowell Institute, Boston, in February, 1933"

Dr Campbell, one of America's outstanding psychiatrists, develops the theme of the personality as an integrated biological unit reacting to the whole environment He begins with its responses to the physico-chemical factors as represented by foods, climate and atmospheric changes, turns to the rôles played by the component parts of the organism—the endocrines, the vegetative and central nervous systems and their influences upon the personality, then swings to the individual's development from its earliest beginnings as an individual to its mature organization as a more or less stable adult, meeting life-situations both within and without

The part played by unconscious factors, the persistence of primitive and childhood views, find their place in the adult. Individual variations are pointed out. The text is illustrated by references to the lives of artists, scientists, philosophers and men of letters, notably Darwin, Beethoven and Schopenhauer.

This is a well written book, and one which is important to anyone who has any interest in the patient as a person, not as a vehicle for pathology.

H M M

Murrell's *What to Do in Cases of Poisoning* By P HAMILL, M D, D Sc, F R C P, Lecturer on Pharmacology and Therapeutics, St Bartholomew's Hospital Medical College, Senior Physician to the Metropolitan Hospital. 208 pages, 10.5 × 16.5 cm. Paul B Hoeber, Inc, New York. 1934. Price, \$1.50.

This pocket-sized manual represents the fourteenth edition of a treatise on poisoning which was first published by the late Dr W Murrell in 1881 and which has been carried on by Dr Hamill since 1921. To facilitate reference the book has been completely reset in larger type and page.

The initial sections on Classification, Antidotes, Emetics, etc., and especially on Diagnosis of Poisoning, are excellent in their terse but adequate presentation. The body of the volume comprises a discussion first of acute, then of chronic poisonings, arranged in alphabetical order. It includes symptoms, fatal dose and treatment. The index is satisfying in its completeness.

While it is understood that brevity must be the very soul of such a treatise, many will feel that in certain instances the author has over-reached himself in this respect. Thus, no mention is made of the efficacy of calcium in quieting the acute phases of lead poisoning, there is no allusion to the use of methylene blue intravenously in cyanide poisoning, the forcing of large quantities of fluids in acute mercurial poisoning is not mentioned—a point now being universally stressed, the treatment given for methyl alcohol poisoning is inadequate. No mention is made of the possible severe acidosis or of increased spinal fluid pressure—the appropriate treatment of which may save the patient's sight or life.

There is a real need for a volume of this size and price and if it can manage to be concise, yet at the same time sufficiently inclusive and up to the times, it will undoubtedly enjoy wide popularity.

H R P

A Text-Book of Pathology By WILLIAM BOYD, M D, M R C P, F R C P, Professor of Pathology in the University of Manitoba. Second edition. 1047 pages, 16 × 24 cm. Lea and Febiger, Philadelphia. 1934. Price, \$10.00.

This book represents the revision of a first edition which appeared in 1932. The division of the book into two parts, viz. General Pathology and Special Pathology, is retained. The subject matter under general pathology is presented in a more logical order than is usual so that the reader, particularly the student, is made acquainted with the important facts concerning disorders of metabolism and local disturbances in the circulation as an introduction to the study of inflammation and repair.

New material has been added to the text, notably on the subjects of Von Gierke's glycogen storage disease, lead poisoning in children, medionecrosis of the aorta in its relation to dissecting aneurysm, renal architecture in chronic nephritis and recent studies of encephalitis.

Although a considerable number of new illustrations is presented, future editions might be improved by further additions, especially in the matter of tumors.

References for additional reading have been extended and they are, for the most part, well chosen. Since the book covers rather thoroughly the common as well as

the more unusual diseases, the brief discussions of certain subjects apparently represent an effort on the part of the author to keep the book within the limits of a single volume

H R S

Clinical Pathology of the Jaws By KURT H THOMA, D M D, Boston, Mass 643 pages, 17 X 25.5 cm Charles C Thomas, Baltimore 1934 Price, \$9 00

In this day of increasing interest in cancer and allied diseases, any book amplifying our knowledge by condensing masses of accumulated data is a welcome adjunct to medical literature. This is especially true in the understudied field of oral surgery—the “No Man’s Land of the human body”—as the author terms it. Although there are many developmental abnormalities of the jaws as well as infections, injuries, fractures, endocrine and nutritional disturbances, nevertheless tumors of the jaws, benign and malignant, take a huge toll in the number of oral cases seen in clinic and private practice. Chronic inflammation from badly kept teeth, dental caries and tobacco, add to the neoplasms of congenital origin to increase the high percentage of mouth malignancies. This the author emphasizes by devoting 481 pages to neoplasms and like lesions, out of a total of 629 pages of text. Sufficient space, however, is given to congenital abnormalities, infections, fractures and other diseases.

The book is bound in dark blue cloth binding and printed on good glazed paper with moderately easy reading type. There are 423 illustrations including photographs of patients, roentgenograms and numerous photomicrographs, some in colors. The free use of photomicrographs is of great value—an adjunct frequently overlooked in many texts. Unfortunately there is no list of illustrations.

The author “treats of physical, roentgen, and microscopic examination, applying the findings to diagnosis and treatment,” correlating data gleaned from a large number of sources including 12 hospitals and dispensaries in America and one in Europe. The repeated use of case histories, especially since these histories are indexed in the back of the book for practical illustration, is helpful. At the end of each chapter there is an ample bibliography.

A short but useful appendix of routine laboratory stains and a general index are given.

In order to make available, at a low cost, a book so extensively illustrated, especially one with so many photomicrographs, a grant was obtained from the Milton Fund of Harvard University.

G E W

Wish Hunting in the Unconscious By MILTON HARRINGTON, M D 189 pages, 13.5 X 19.5 cm Macmillan Company, New York 1934 Price, \$2.50

“Most of us are too busy taking care of our own personal affairs or advancing some cause with which we are identified to spare much time on the thankless task of trying to pull down other people’s houses.”

Dr Harrington feels that psycho-analysis is a structure which should be razed, and his own erected in its place. He does not believe that behavior is a response to emotional demands, but is “made up of two different kinds of action (1) Movements or changes of position, which are produced by the muscles, and (2) chemical changes, which are produced by the glands.” He considers analysis a form of suggestion which sees in each problem exactly what the analyst is looking for, and in which the patient is inclined to give up his symptoms and accept an explanation for them, whether or not that explanation is true, because of the patient’s love for the analyst. Resistance is only a convenient way of avoiding explanations which the analyst is unwilling to give or which interfere with his views. Breaking it down is breaking down the patient’s critical judgment and common sense. In accepting thoughts or

fantasies as valid items of experience, the analyst manufactures evidence to support his theory. Analysis itself is a species of religious conversion, blinding its devotees to truth. Its popular success is based partly upon the strength of this, partly because it explains everything and partly because it "includes a thrilling sexual experience thrown in." In short it is an "expensive long drawn-out course of muck taking for pervert sexual desires in the cesspool of the unconscious."

The antagonism apparent throughout leads one to discredit its validity as a critical work. The author's own alternative theory is unsatisfactory. No evidence is brought forth to support his views.

H M M

COLLEGE NEWS NOTES

NEW LIFE MEMBERS OF THE COLLEGE

The following Fellows of the College have become Life Members by contributing the specified fees to the Endowment Fund of the American College of Physicians

| | |
|--|------------------|
| Dr Joseph M King, Los Angeles, Calif | January 21, 1935 |
| Dr Win J Stapleton, Jr, Detroit, Mich | January 21, 1935 |
| Dr George E Baxter, Chicago, Ill | January 22, 1935 |
| Dr Clifford E Henry, Minneapolis, Minn | March 8, 1935 |

Acknowledgment is made of the following gifts to the College Library of publications by members

Dr Wilburt C Davison (Fellow), Durham, N C—one book, "The Compleat Pediatrician",

Dr Ralph O Clock (Fellow), New York, N Y—one reprint,

Dr Harold Swanberg (Fellow), Quincy, Ill—four reprints,

Dr Frederick R Taylor (Fellow), High Point, N C—two reprints,

Dr Felix J Underwood (Fellow), Jackson, Miss—one reprint,

Dr S Arthur Weisman (Fellow), Minneapolis, Minn—nine reprints,

Dr Ralph M Fellows (Associate), Topeka, Kansas—one reprint,

Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint,

Dr Rafael Rodriguez-Molina (Associate), San Juan, P R—six reprints,

Dr P H Sprague (Associate), Edmonton, Alberta, Can—one reprint

A Round Table Clinic Day was held by the Fellows and Associates of the American College of Physicians residing in western Pennsylvania, and surrounding country, at the Falk Clinic on February 22, 1935. The members were called together by Dr E Bosworth McCreedy, Governor of the College for western Pennsylvania, and the program was arranged by Dr Joseph H Barach, Dr John M Thorne and Dr Clement R Jones, Chairman, all of Pittsburgh. Members were present not only from the western Pennsylvania towns, but from Wheeling, Fairmont and Youngstown.

Dr Joseph H Barach gave a clinic on diabetes, Dr Clement R Jones a clinic on syphilis of the stomach, and members of the Falk Clinic staff gave additional clinics on peptic ulcer and migraine. The discussions were general and interesting. The group voted to suggest that such a meeting be held twice a year in the future.

Dr W R Houston (Fellow and Governor of the College for the State of Georgia) has removed from Augusta and established practice in Austin, Texas.

Dr William Gerry Morgan (Fellow) and Dr Hugh S Cumming (Fellow) addressed a special public meeting of the District of Columbia Tuberculosis Association, Washington, D C, on March 30, 1935, on "Modern Medical and Surgical Treatment" and "Coordinating Public and Private Health Agencies to Control Tuberculosis," respectively.

Dr George Adams Merrill (Fellow), Brooklyn, N Y, was recently elected Director of Medicine and President of the Medical Board of the Kings County Hospital. He is also President of the Brooklyn Society of Internal Medicine for the present year.

Dr C Walter Clarke (Fellow) has been appointed by the Office of Indian Affairs, United States Department of the Interior, a Special Consultant on Syphilis. Dr Clarke is conducting a series of lecture demonstrations for the medical personnel of the Indian Service and will initiate epidemiological studies of syphilis among the Indians

Dr Conrad Wesselhoef (Fellow), Associate in Communicable Diseases at Harvard Medical School, has received from the War Department the Oak Leaf Cluster for extraordinary heroism in establishing and operating a first-aid station near the front line trenches, under intense machine gun and artillery fire, from July 18 to 28, 1918. Dr Wesselhoef went overseas with the 26th Division, and was promoted to Captain. He served in the following engagements: Chemin des Dames sector, La Reine sector, Chateau-Thierry, Saint-Mihiel, and Meuse-Argonne offences, and received the Distinguished Service Cross and the Croix de Guerre and was twice cited in general orders, Headquarters, 26th Division—*Harvard Alumni Bulletin*, February 8, 1935

Dr Lyell C Kinney (Fellow), San Diego, Calif., is a Vice-President of the American Roentgen-Ray Society for the present year

Dr David Riesman (Fellow), Philadelphia, Pa., is President-Elect of the Interstate Postgraduate Medical Association

Dr Edward B Vedder (Fellow), Washington, D C., is the President of the American Society of Tropical Medicine

Dr Jacob C Geiger (Fellow), Health Officer of San Francisco, is President of the San Francisco County Medical Society

Dr Clarence E Simonds (Fellow), Willimantic, Conn., has been appointed Health Officer of Windham, Conn

Dr John A Kolmer (Fellow) has been placed in charge of a new department for research on bacteriophage at Temple University Hospital, Philadelphia

Dr Lewellys F Barker (Fellow), Baltimore, Md., delivered the Beaumont Lectures of the Wayne County Medical Society, Detroit, Mich., February 4 to 5 on "Heredity and Environment in Relation to the Handicapped." Dr Barker also addressed the Wayne University Medical School students, February 5, on "Major and Minor Medical Morals"

The University of Michigan has recently established a division of health sciences as an advisory unit of the institution. It will include the Medical School, School of Dentistry, Division of Hygiene and Public Health, School of Nursing, College of Pharmacy and the Department of Postgraduate Medicine. Dr James D Bruce (Fellow and Governor), who is Vice-President of the University and Head of the Department of Postgraduate Medicine, has been named Chairman of the newly created division.

Dr Carl V Weller (Fellow), Professor of Pathology, and Dr Udo J Wile (Fellow), Professor of Dermatology, have been named members of an Executive Committee for the division

Dr James Burns Amberson, Jr (Fellow) has recently been appointed Assistant Professor of Clinical Medicine at the New York University and Bellevue Hospital Medical College

Dr Charles James Bloom (Fellow), New Orleans, read before the Southern Medical Association in San Antonio on November 16, 1934, a paper entitled "Thyrototoxicosis in Children"

OBITUARIES

EDGAR MOORE GREEN

Dr Edgar Moore Green (Fellow), born in September 1862, died March 9, 1935. He was a son of the late Dr Traill Green and Harriet Moore Green. On his maternal side he was a descendant in the eighth generation of John and Priscilla Mullins Alden. He received his early education in public and private schools, graduating from Easton High School in 1879. He entered Lafayette College where he was one of the Junior orators, won the mathematical, astronomical and Early English Text Society's prizes and was graduated in the class of 1883, delivering the honorary oration in astronomy. He received his medical degree in 1886 from the University of Pennsylvania, being awarded the prize for the highest average. From 1895 to 1897 he was pathologist to St Luke's Hospital, Bethlehem, Pa. He was a member of the Board of Trustees of Lafayette College. From 1904 to 1924 he was Physician-in-Chief to the Easton Hospital. He was consulting internist to St Luke's Hospital, Bethlehem, Norristown State Hospital, and Warren Hospital, Phillipsburg, N. J. He was a member of the Advisory Board of the State Department of Health and also a member of the State Board of Medical Education and Licensure. He held membership in the Phi Kappa Psi, Alpha Mu Pi Omega, and Phi Beta Kappa fraternities. He was a member of the Northampton County Medical Society, the Medical Society of the State of Pennsylvania, the American Medical Association, and the Philadelphia Pathological Society. In 1917 he received the honorary degree of Doctor of Science from Pennsylvania College at Gettysburg, Pa. In 1924 he became a Fellow of the American College of Physicians.

Had Dr Green lived but ten days longer he would have seen the completion of a century of continuous service rendered by his father and himself in the field of medicine in Easton. He was uniformly courteous and kindly. He was beloved by all who knew him. His passing leaves a gap which will be difficult to fill.

FRANCIS J. DEVER, M.D., F.A.C.P.

STEPHEN LIVINGSTON TAYLOR

Dr Stephen Livingston Taylor, Associate of the American College of Physicians since 1925, died in the Faulkner Hospital, Boston, Massachusetts, of heart disease, January 29, 1935, aged 66 years.

Dr Taylor was a graduate of Amherst College and received his medical degree from the College of Physicians and Surgeons of Columbia University in 1894. He pursued postgraduate study at the Trudeau School of Tuberculosis. From 1904 to 1914 he was attending physician to the Brooklyn Orphans' Asylum, from 1906 to 1912, assistant surgeon to the Methodist Episcopal Hospital, and for many years, attending physician to the Broad Street Hospital of Oneida, N. Y. Dr Taylor was also the health officer of Sherrill for a long period of years. He was a member of his county and state medical societies, of the National Tuberculosis Association, and a Fellow of the American Medical Association.

JAMES EDWIN CAMPBELL TAYLOR

Dr James Edwin Campbell Taylor (Associate), Columbus, Ohio, died December 12, 1934, of influenza, aged 35 years.

Dr Taylor was born at Columbus, Ohio, December 5, 1899. He held the degrees of A. B. (1921) from Harvard University and Doctor of Medicine (1928) from the Ohio State University College of Medicine. He was medical intern at the Kings County Hospital, Brooklyn, N. Y., for one and one-half years and concluded a two-year medical Fellowship at the Mayo Clinic. Afterwards, he became Assistant in the Ohio State University College of Medicine. He was a member of the Attending Staff of Mt. Carmel and St. Francis Hospitals and a member of the Visiting Staff of the White Cross and University Hospitals. He was elected an Associate of the American College of Physicians during 1932.

HARRY SAMUEL WAGNER

Dr Harry Samuel Wagner (Fellow), Pocasset, Massachusetts, died February 8, 1935, in the Baker Memorial Hospital, Boston, aged 57 years.

Dr Wagner was born in Toledo, Ohio, June 4, 1877. He received the degree of Ph. B. from Denison University in 1899 and the degree of Doctor of Medicine from the University of Michigan Medical School in 1903. He was Assistant Superintendent of the Westfield State Sanatorium from 1910 to 1912, Superintendent of the Hartford State Sanatorium from 1912 to 1916, Superintendent of the Pressmen's Sanatorium from 1916 to 1919, and had been Superintendent of the Barnstable County Sanatorium, Pocasset, Massachusetts, since 1919.

Dr Wagner was a member of the Barnstable County Medical Society, Massachusetts Medical Society, National Tuberculosis Association, American Sanatorium Association, Trudeau Society of Boston, and a Fellow of the American Medical Association. Dr Wagner became a Fellow of the American College of Physicians during 1929.

HIRAM DAVIS LAWHEAD

Dr Hiram Davis Lawhead (Associate), Woodland, California, died November 29, 1934, of coronary occlusion, aged 82 years

Dr Lawhead was indeed a distinguished member of his community, and his deeds of goodness to the people and his support of cultural activities for the community were outstanding. He was a school teacher for a number of years, then studied medicine at Cooper Medical College, San Francisco, graduating in 1883. He began practice at Knights Landing, but in 1887 located at Woodland, and practiced there continuously for forty-seven years.

Dr Lawhead contributed several worthwhile articles to the medical literature, more especially one upon the "Art of Medicine" in 1926. He was a charter member of his local county medical society, the Yolo-Colusa-Glenn Society for Medical Improvement, and served as president, as well as secretary, for several years. He was likewise a charter member and president for one year of the Northern District Medical Association of California, a member of the California Medical Association, and a member of the American Medical Association. He became an Associate of the American College of Physicians in 1922.

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MALIGNANT MONOBLASTOMA

A VARIANT OF MONOCYTIC LEUKEMIA *

By LOUIS A. MITCHELL, M.D., *Newark, Ohio*

IN 1913 Reschad and Schilling-Torgau¹ reported the first case of monocytic leukemia to appear in the literature. Since then the disease has gradually gained recognition, and variations from its usual form, such as are found in association with other types of leukemia, have been observed. However, extensive tumor formation with primary multiple monoblastomata of the connective tissues ending in a terminal leukemic phase in which large numbers of primitive monoblasts flooded the peripheral circulation, such as is herewith described, has not previously been reported.

The acceptance of monocytic leukemia as a distinct disease has come through a recognition of the monocyte as an independent cell entity. The theory of cell relationship which advances this view is now generally accepted among hematologists, although other theories still find their adherents.

THE ORIGIN OF THE MONOCYTE

The method of formation of this cell has been one of the most controversial points in hematology. At least 19 different theories of the origin of the monocyte have been suggested², of these the following have been given the widest recognition.

The unitarians (Maximow³) believe that the monocyte, in common with the other blood cells, takes its origin from the lymphocyte. All stages of transition from the small lymphocyte to the adult monocyte are described as occurring both in the circulating cells of the blood and among the resting cells of the tissues. They see in the lymphocyte an element which is relatively undifferentiated as to structure and function and which exists solely to produce other blood cells.

The dualists (Naegeli⁴) recognize two independent series of leukocytes. They believe that the monocyte is of myeloid origin, developing from the myeloblast, while the lymphocyte is an independent cell type.

* Received for publication January 8, 1935.

From the Pathological Laboratories of the Newark City Hospital, Newark, Ohio.

The generally accepted view today is that of the modified dualists (Cunningham, Sabin, and Doan⁵) These observers recognize three types of leukocytes, each with its own characteristic hematopoietic tissue, which arise from a common mesenchymal rest and stem cell Just as the granulocytes normally come from myeloid tissue in the bone marrow and lymphocytes from lymphatic tissue in the lymph nodes, spleen, and diffuse lymphoid tissue of the body, so the monocyte arises in the connective tissue from so-called histiocytes of the reticulo-endothelial system The development of the leukocytes of each series from a common stem cell is an irreversible process once the specific blast stage is reached The structure and function of the reticulo-endothelial system is of particular interest in explaining the origin of the monocyte according to this theory

The cells which compose the reticulo-endothelial system are probably as close to primitive embryonic mesenchyme as occurs in the adult body They form the stroma of the lymphoid and myeloid tissue In the stroma they occur as a reticulum whose cells flatten out to line the lymph and blood spaces where they are known as "endothelial" or "littoral" cells In all diffuse connective tissues of the body they are found in close relation with fibrous tissue cells whose number they almost equal Hereafter these connective tissue elements will be referred to as "tissue histiocytes" In the resting state they appear as dense elongated nuclei whose cytoplasm can not be identified When activated they are large cells whose abundant cytoplasm is highly phagocytic The morphological identity of the cells of this system is not always evident and they are primarily grouped on a functional basis Their distinctive behavior is the storage of certain colloidal dyes when these dyes are injected into the body in a more dilute solution than can be taken up by any other cells of the organism However, it is the function of hematopoiesis which is of immediate interest Sabin, Doan, and Cunningham,⁶ as a result of supravital studies, have described two types of wandering cells which take their origin from the reticulo-endothelial system the clasmatocyte, or tissue macrophage, and the monocyte They believe that the clasmatocyte takes its origin from the "endothelial" lining of the blood and lymph spaces This is a large cell which is characteristically found in the tissue where it participates in local inflammation and takes up coarse debris, such as damaged red blood cells and products of tissue necrosis The monocyte, which arises from the histiocyte of the diffuse connective tissues, is a smaller cell, also found in the connective tissues but maintained at a relatively constant level in the circulating blood This cell is also phagocytic but takes up finer particulate matter than the clasmatocyte and has an affinity for lipoids Other observers believe that these two cells, while morphologically and functionally distinct, represent two phases in the life cycle of a single cell type, and the results of tissue culture tend to confirm this view

CASE REPORT

A white male, aged 63, a railroad engineer by occupation, was first seen on April 1, 1932, when he complained of general weakness and persistent abdominal distention and discomfort. In the past he had always been in good health and had led an active life. About the first of December 1931 he noticed that he lacked his usual strength and energy. He first consulted a physician in March and at this time he was told that he was anemic. He noticed a slightly palpable, reddish eruption on the inside of the calf of each leg and the lower thigh. In addition to this a few small subcutaneous nodules were noted on the lower abdomen which later spread over the trunk, arms, and the region of the scalp. With the appearance of these nodules tenderness of both testicles was complained of. Up to the time that he presented himself for examination he had no relief from any of his symptoms and there had been a gradual increase in the number of subcutaneous nodules.

Examination. The patient was a man of small stature, of adipose muscular type. His height was 5 feet $4\frac{1}{2}$ inches, weight 124 lbs., pulse rate 80, temperature 98° F., blood pressure 120 systolic and 70 diastolic. There was evidence of slight loss of weight. General nutrition was fairly good, although the skin and mucous membranes had a pale, pasty appearance. The gums were in good condition. The skin and mucosae were free from petechiae. There was a maculo-papular eruption of numerous dark red, more or less confluent lesions covering an area the size of the palm of the hand above and below the knee on the inside of each leg. Their color did not blanch on pressure and the eruption was evidently due to an intracutaneous infiltration. About 200 pea-sized, subcutaneous nodules were distributed over the trunk, arms, and upper third of the thighs. These nodules were firm, discrete, and freely movable in the subcutaneous fat, although a few of them were attached to the dermis. Where the nodules were attached, the surface of the skin had a reddish discoloration which could not be pressed out. Ten slightly larger, hemispherical nodules were adherent to the periosteum of the skull. The scalp was freely movable over these nodules. The face and forehead were free from lesions. The lymph nodes showed no significant adenopathy. The tonsils were small, irregular, and free from congestion. The liver and spleen were not enlarged either to percussion or palpation. There was a slight, uniform distention of the abdomen with diffuse tenderness on palpation. The prostate was normal in size and contour, and microscopic examination of its secretion was negative. Both testicles were normal in size, contour and consistency. There was a moderate, uniform, firm enlargement of each epididymis which was quite tender. The bones and joints were normal. Neurological examination was negative.

The patient was referred to a dentist who, after radiographic examination of all teeth, reported that there was no oral sepsis. Later an infected molar was found which was extracted. This was followed by slight oozing for 24 hours. The blood clotting time was three minutes.

Radiographic examination of the bones of the pelvis and lower spine was negative. The urine was essentially negative.

Treatment and progress. (Two subcutaneous nodules were removed for biopsy from the anterior chest wall on April 11). The injection of arsenic in the form of sodium cacodylate, gr $\frac{3}{4}$, subcutaneously every second day was begun on April 4 and continued at this interval until July 8. There was a very striking improvement in the patient's symptoms after a few of these injections. He no longer suffered from abdominal discomfort and noticed a definite return of strength and energy. At the same time the maculo-papular eruption on the legs rapidly disappeared, leaving a brownish pigmentation of the skin. The subcutaneous nodules were reduced to not over 25 in number. Then, without any change in the subjective symptoms, the nodules increased rapidly in number until there were about 100 of them. At the same time

the testicles enlarged to twice their normal size, while the epididymis remained moderately enlarged as previously noted. The Aschheim-Zondek test was negative.

Radiation of the testicles and nodules was begun on May 10. As the result of one exposure each testicle and epididymis was reduced to a small, irregular, firm mass not over 2.5 cm in its greatest diameter. The subcutaneous nodules which were directly radiated disappeared promptly, so that after 11 exposures to radium and roentgen-ray over a period of three weeks only 10 nodules were present. (On May

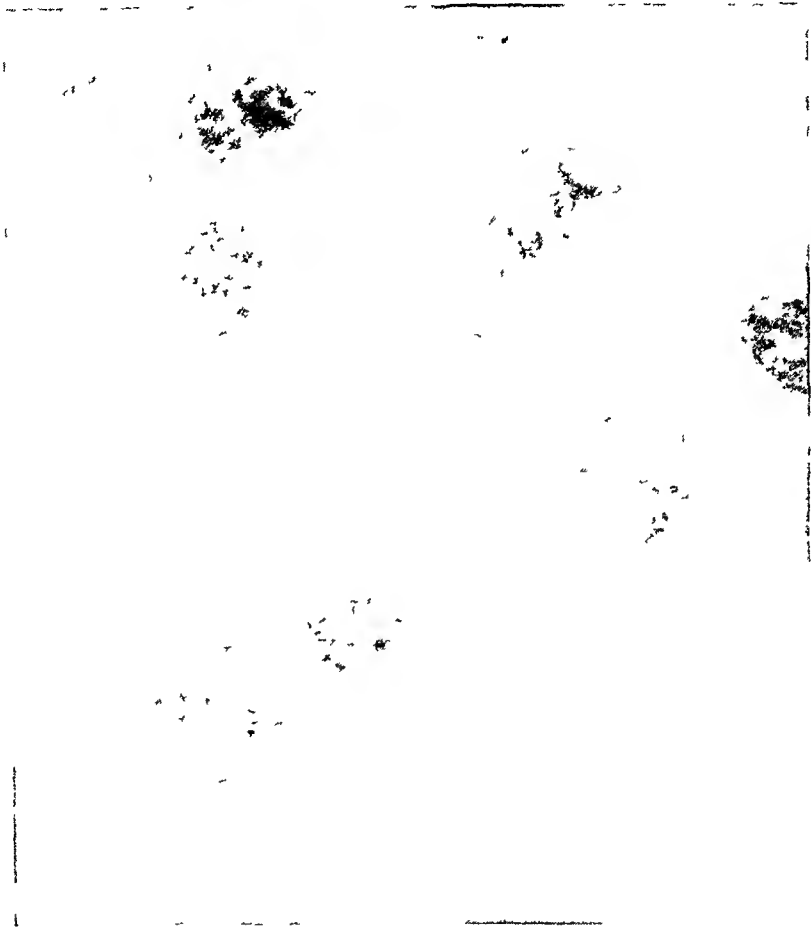


FIG 1. Peripheral blood smear, Wright's Giemsa stain $\times 900$. *Monoblasts*. These cells have thin irregular borders. Their cytoplasm has a cloudy appearance and often contains innumerable dust-like azurophilic granules. Its staining reaction is moderately basophilic. The nuclei are eccentrically placed, and are round, oval, or bean-shaped.

15 two subcutaneous nodules, neither of which was directly radiated, were removed for a second biopsy.)

On July 8 it was noted that the number of nodules had increased definitely in spite of continued radiation and administration of arsenic. The patient complained of a return of general weakness. This marked the beginning of the final exacerbation of the disease. Abdominal discomfort and flatulence returned and persisted. Roentgenographic examination of the stomach and intestines showed no evidence of any

MALIGNANT MONOBLASTOMA

pathologic lesion. A chest roentgenogram at this time appeared essentially negative. On July 21 an elevation of temperature, varying around 101°F , was noted. This persisted without change up to the terminal hyperpyrexia. Demonstrable enlargement of the liver and spleen occurred during the final 10 days of the illness. The liver extended more than three fingers breadth below the costal margin and retained its normal contour. The spleen was just palpable at the costal margin. There was never any palpable enlargement of the lymph nodes. Shortly after enlargement of

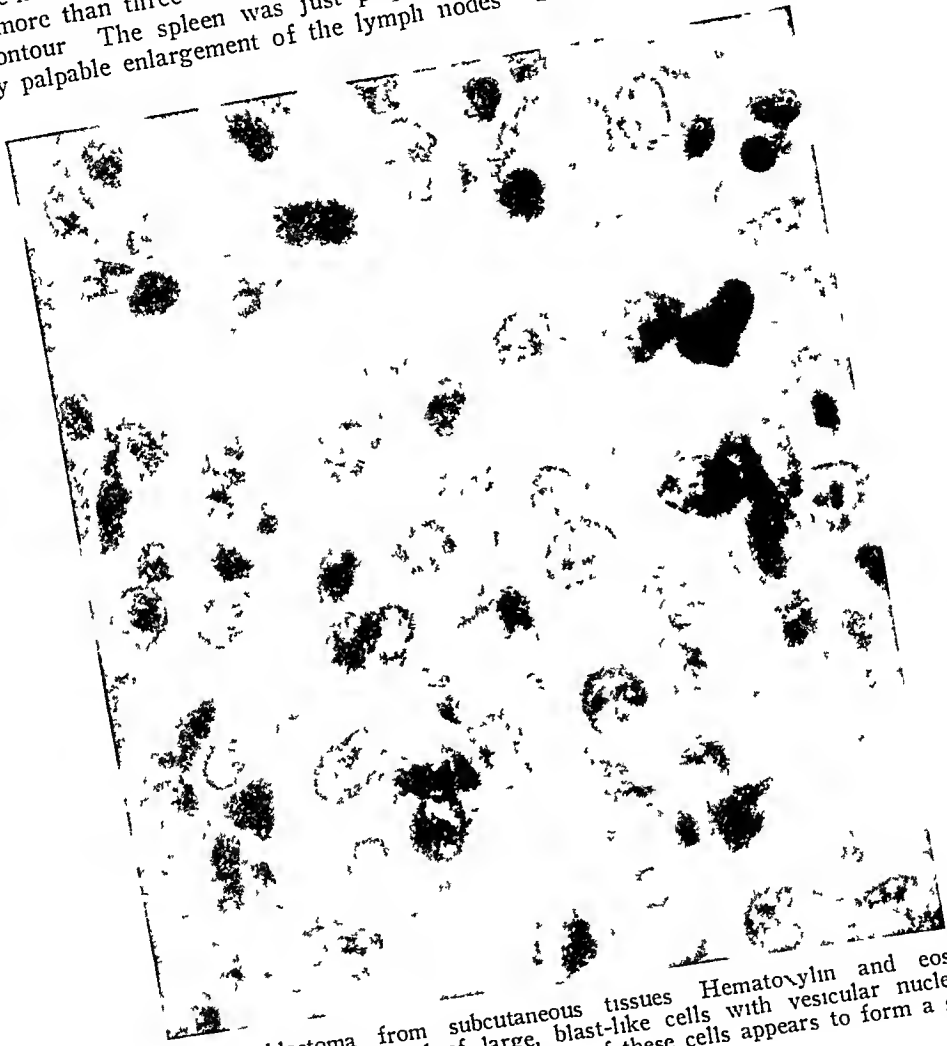


FIG 2 Monoblastoma from subcutaneous tissues. Hematoxylin and eosin stain $\times 900$. The nodule is composed of large, blast-like cells with vesicular nuclei and an occasional prominent nucleolus. The cytoplasm of these cells appears to form a syncytium. A few small lymphocytes are present.

the liver and spleen was noted there was oozing of blood from the gums and repeated small hemorrhages of bright red blood from the bowels. Multiple small areas of submucous and subcutaneous hemorrhage also made their appearance. Administration of arsenic and irradiation were discontinued on July 8, but after this there was no striking increase in the number of nodules, although they individually grew to a slightly larger size. About two dozen were present at the time of death and the largest nodule measured 1.5 cm in diameter. One nodule involved the periosteum of the lower end of the sternum. The leukemic blood picture was first noted on August 3. There was never any marked loss of body weight and no cachexia.

The behavior of the nodules during the course of the disease was interesting. The patient noticed no tendency for them to disappear spontaneously until treatment was begun. Their temporary response to the administration of arsenic was striking and they were very radiosensitive. There was a constant tendency for new nodules to appear even when the older ones were disappearing most rapidly under treatment. Their growth seemed to be under some degree of control, since they never increased



FIG 3. Section from the periphery of the same nodule as figure 2. Foot's reticular stain $\times 100$. This section shows that the number of argyrophil fibers present varies directly with the number of monoblasts in any part of the section.

greatly in size or infiltrated beyond the periosteum or subcutaneous fat in which they originated.

Examination of Tissue Removed at Biopsy. April 11, 1932. Two nodules were removed each of which was the size of a large pea. One shelled out from the surrounding fat with a smooth surface but showed no evidence of a capsule. The borders of the second nodule merged into the surrounding adipose tissue without any line of demarcation. The cut surface of both nodules was firm and elastic and pinkish-gray in color. The section stained with hematoxylin and eosin showed large blast-like cells infiltrating fat (figure 2). There was a moderate amount of cytoplasm but no cell outline could be made out. A few of the cells contained a little fine phagocytized material. They had large malignant looking vesicular nuclei which

were round, oval, or deeply indented and varied greatly in size. They often contained one nucleolus. Many cells contained mitotic figures. There were no giant cells present. There were a very few adult lymphocytes scattered throughout the section, and a very few collagen fibers were present. There was no evidence of hypervascularization of the tissue.

Sections of the nodules were referred to a number of pathologists. At this time the majority regarded the growth as malignant blastoma although the possibility of carcinoma and sarcoma was also suggested.

With Foot's reticular stain numerous fine argyrophyl fibers were demonstrated in the nodule. These fibers were more numerous toward the center of the nodule where the infiltrating cells were closely packed and they followed the cords of cells toward the periphery (figure 3).

May 13, 1932. Two subcutaneous nodules were removed. They were similar grossly and microscopically to the nodules described above.

DESCRIPTION OF THE BLOOD

Dr. C. A. Doan saw this patient in the different phases of his illness and Doan and Wiseman¹⁰ have referred to the leukemic manifestations of the case in the report of a series of cases of monocytic leukemia which have come under their observation. The present detailed analysis of the case has been made in cooperation with these investigators and with their concurrence in the interpretations of biopsy and postmortem material.

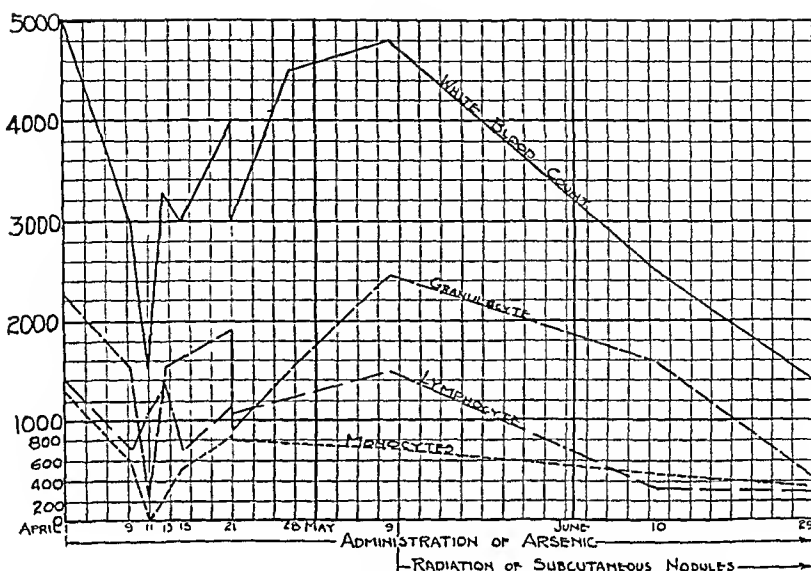
The differential counts were made from fixed smears with Wright's stain and by the supravital method.

The disease had two phases. The aleukemic phase lasted seven months after the onset. The onset of the leukemic phase probably coincided with the appearance of the terminal exacerbation of the disease three weeks before death, but was not demonstrated until one week before death.

In the aleukemic phase all of the leukocytes were mature. From the first there was a relative increase in monocytes in the blood with their absolute count normal or slightly reduced (Table 1 (A)). The dramatic response of all of the leukocytes in the peripheral blood to the administration of arsenic was coincident with the rapid disappearance of the subcutaneous nodules, marked clinical improvement, and improvement in the anemia (Chart I). After two injections of sodium cacodylate there was a sharp reduction in the total number of granulocytes, the monocytes for a short time disappeared from the peripheral blood, while there was comparatively little change in the absolute number of lymphocytes. The administration of arsenic was continued but its effect on the blood picture was even more temporary than its effect on the nodules. There was a slight, rather uniform reduction in the number of all of the leukocytes when the subcutaneous nodules were dissolved by irradiation. At this time the monocytes were less affected than the cells of any other series (Chart I).

In the leukemic phase very primitive white blood cells, which were identified as monoblasts, dominated the blood picture (Figure 1 and table 1 (B)). These cells varied in size from 12 to 30 micra and the average cell was large. The nuclei stained a reddish-purple with Wright's Giemsa stain. They occupied practically the entire cell in some cases, in others they constituted only a little over a third of the cell volume. The nuclei characteristically assumed an eccentric position. The cytoplasm had an opaque, bluish-grey appearance and was much darker in some cells than in others, due apparently to the increased amount of basophilic spongioplasm present. The cytoplasm of about one-half of the cells contained innumerable fine bluish-red granules. There was a varying number of small clear vacuoles present in some cells. A very occasional cell contained phagocytized material, which consisted either

CHART I



EFFECT OF THERAPY OF THE LEUKOCITES OF THE PERIPHERAL BLOOD

Sodium cacodylate, gr 3/4, was administered hypodermically during the entire period of time represented by the curves. In addition to this the subcutaneous nodules were radiated with radium and roentgen-ray beginning May 10. Coincident with the administration of arsenic there was marked clinical improvement and improvement in the anemia.

of coarse particles or degenerated erythrocytes. The cells were round or oval, usually very irregular in outline. Their borders were sometimes smooth but often were very uneven, due to numerous small protoplasmic projections which gave the edge an irregular, scalloped appearance. Occasionally there was a larger pseudopod-like projection. The nuclei were usually spheroidal or oval in shape and occasionally indented, while a few were irregular. The chromatin was arranged in a fine, skein-like network without pattern. One or two nucleoli were often present. In a few cells there was a bud-like projection of the nucleus. Degenerated nuclei, with or without protoplasm, constituted over 10 per cent of the cells. Non-nucleated cytoplasmic bodies of varying size were present. A few cells were undergoing amitotic division. Adult monocytes were very rarely seen and disappeared completely with the marked increase in the immaturity of all of the leukemic cells in the last count made 30 hours before death. The peroxidase reaction of these cells was not satisfactorily determined. A very few typical myelocytes were present. All lymphocytes were small and distinctly adult in type.

On supravital examination the predominating cell in the leukemic phase varied markedly in individual size. The cytoplasm was not clear, but had a mottled, greyish background in which was found a moderate number of fine bluish-green mitochondria. Many of these cells contained no neutral red vacuoles but those which did showed a typical arrangement about a clear area representing the centrosome, and were located just at one side of the nucleus. No motility was observed in any of the cells belonging to the monocytic series. No specific granules were present in any cells except those which were unquestionably myelocytes, of which there was a very minimal number.

A moderately severe secondary anemia persisted throughout the entire period. The red blood cells averaged seven micra in diameter. Occasional normoblasts were

TABLE I
A Aleukemic Phase

| A. Aleukemic Phase | | | | | | | | | | | | | | | | | | |
|--------------------|-----|-------|-------------|---------------|-----------------------|-----------|--------------------------|-------|--------------|-----|----------|-----|------|-------|-----------|-------|-------|-------|
| Date, 1932 | Hgb | R B C | Color Index | Reticulocytes | Erythrocyte Fragility | Platelets | Sedimentation Time, 1 hr | W B C | Differential | | | | | | | Total | | |
| | | | | | | | | | Neut | Lym | Monocyte | Eos | Base | Class | Myelocyte | Neut | Lym | Mono |
| 4-1 | 40 | 5 | | | | | | 5,000 | 45 | 28 | 26 | | 1 | | | 2,300 | 1,400 | 1,300 |
| 4-9 | | | | | | | | 3,000 | 55 | 25 | 20 | | 1 | | | 1,650 | 750 | 600 |
| 4-11 | 40 | 30 | | 2% | | 60,000 | | 1,500 | 18 | 82 | 0 | | | | | 270 | 1,230 | 0 |
| 4-13 | 37 | 34 | | | | | | 3,300 | 46 | 45 | 8 | 1 | | | | 1,518 | 1,485 | 264 |
| 4-15 | 40 | 31 | | | | | | 3,000 | 52 | 24 | 19 | 1 | 1 | | | 1,560 | 720 | 570 |
| 4-21 | 42 | 37 | | 2% | 0 300 0 369 | 160,000 | 20 mm | 4,000 | 45 | 32 | 22 | 1 | | | | 1,800 | 1,280 | 880 |
| | | | | | | | | | 30 | 40 | 28 | 2 | | 2 | | 900 | 1,200 | 840 |
| 4-21 | 43 | 30 | 66 | | | | | 3,000 | | | | | | | | | | |
| 4-28 | 55 | 33 | | | | | | 4,500 | 51 | 30 | 15 | 4 | | | | 2,448 | 1,440 | 720 |
| 5-9 | 50 | 36 | | | | | | 4,800 | 64 | 12 | 18 | 2 | | | | 1,600 | 300 | 450 |
| 6-10 | 50 | 33 | | | | | | 2,500 | 32 | 40 | 26 | 2 | | | | 480 | 600 | 390 |
| 6-29 | 40 | 32 | | | | | | 1,500 | | | | | | | | | | |

B Leukemic Phase

| Date, 1932 | Hgb | R B C | Color Index | Reticulocytes | Erythrocyte Fragility | Platelets | Sedimentation Time | Differential | | | | | | | Total | | | | | | | |
|------------|-----|-------|-------------|---------------|-----------------------|-----------|--------------------|--------------|------|-----|------|----------|-----------|------------|-------|-------|-------|-------|----------|-----------|------------|-------|
| | | | | | | | | Lym | Neut | Eos | Base | Monocyte | Monoblast | Myelocytes | Lym | Neut | Eos | Base | Monocyte | Monoblast | Myelocytes | |
| 8-3 | 40 | 31 | | | 0 319- 0 430 | | | 53,000 | 2 | 1 | | | 1 | 95 | 1 | 1,086 | 530 | 0 | 0 | 530 | 50,350 | 530 |
| 8-4 | | 30 | | | | 60,000 | | 48,000 | 6 | 3 | | | 1 | 81 | 9 | 2,880 | 1,440 | 0 | 0 | 480 | 38,880 | 4,320 |
| 8-5 | 35 | 25 | 77 | 2% | 0 341 0 471 | | | 76,000 | 3 | 3 | 2 | 2 | 3 | 86 | 1 | 2,280 | 2,280 | 1,520 | 2,280 | 2,280 | 65,360 | 760 |
| 8-5 | | 30 | | 6% | | 240,000 | | 130,000 | 1 | 1 | | | 0 | 98 | 0 | 1,300 | 1,300 | 0 | 0 | 0 | 127,400 | 0 |

present. The erythrocyte fragility was normal throughout the aleukemic phase and increased in the leukemic phase. The blood platelets were decreased until the last, when they reached the normal range.

AUTOPSY

Permission was obtained for only a limited examination. There was a marked pallor of the skin and mucous membranes and a slight diffuse edema of the skin. Eight small areas of subcutaneous hemorrhage were scattered over the lower half of

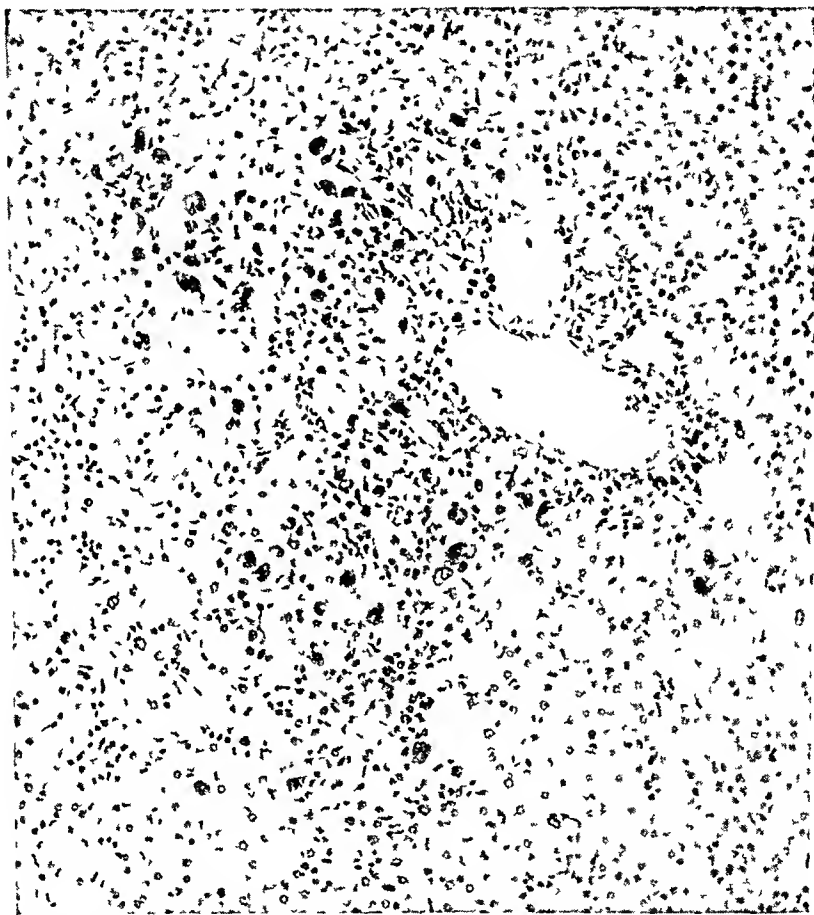


FIG 4. Reticular hyperplasia in the liver. Hematoxylin and eosin stain. $\times 100$. The reticular hyperplasia with many multinucleated giant cells completely replaces the liver cords in a small area at the periphery of a lobule.

the trunk and the thighs. Twenty-two subcutaneous nodules, varying in diameter from 0.5 to 1.3 cm, were present. One nodule was firmly attached to the periosteum of the sternum. There was no enlargement of the superficial lymph nodes. *Abdomen*. The peritoneum was normal. No mesenteric lymph nodes could be palpated. The liver was enlarged about 50 per cent, but retained its normal contour. It was uniformly firm in consistency. The cut surface had a mottled appearance due to a fine, golden-yellow trabeculation on a reddish-brown background. Three or four discrete, whitish, shot-like nodules were embedded in the substance of the liver. The

spleen was about three times the usual size and retained its usual contour. It was very soft and slightly uneven in consistency. The cut surface was dark red and came away very easily on scraping. Both kidneys and ureters, the right adrenal capsule, the pancreas, and the omentum showed no gross abnormality. A section was taken from the eighth and ninth ribs. Their medulla was red in color and firm in consistency. *Subcutaneous Nodule* One nodule which was removed was roughly spherical in shape and measured 0.8 cm. in diameter. The borders merged into the surrounding fat without a definite line of demarcation. The cut surface of the central portion was firm, elastic, and pinkish-gray in color.

Microscopic Examination Liver The capsule was not thickened or infiltrated. The liver cords were thinned and the sinusoids were loosely packed with large mononuclear cells, giant cells, and often with swollen, partly desquamated endothelial cells. There was complete displacement of the hepatic tissue by reticular hyperplasia in areas of varying size (figure 4). Where these areas were small they occurred toward the periphery of the lobule, where they were large they completely displaced several lobules. They were composed of an imperfect reticulum whose stellate cells sent out broad protoplasmic processes often extending from one cell to another (figure 5).



FIG 5 Higher magnification of the reticular area shown in figure 4. Hematoxylin and eosin stain $\times 900$. The section shows an imperfect fragmentary reticulum formed by broad protoplasmic processes extending from one cell to another. Scattered throughout this reticulum are many free mononuclear and giant cells.

There was usually a background of amorphous intercellular substance. The cells of the reticulum usually contained one large vesicular nucleus, but occasionally up to five or six separate nuclei were included in a large protoplasmic mass. Many free mononuclear cells and multinucleated giant cells were scattered throughout this incomplete reticulum. These areas had a loose structure which was continuous at its margins, between gradually thinning liver cords, with the contents of the sinusoids. Mitotic figures were rarely seen in the free cells and never in the cells of the reticulum. Microscopically the shot-like areas mentioned in the gross were composed of closely

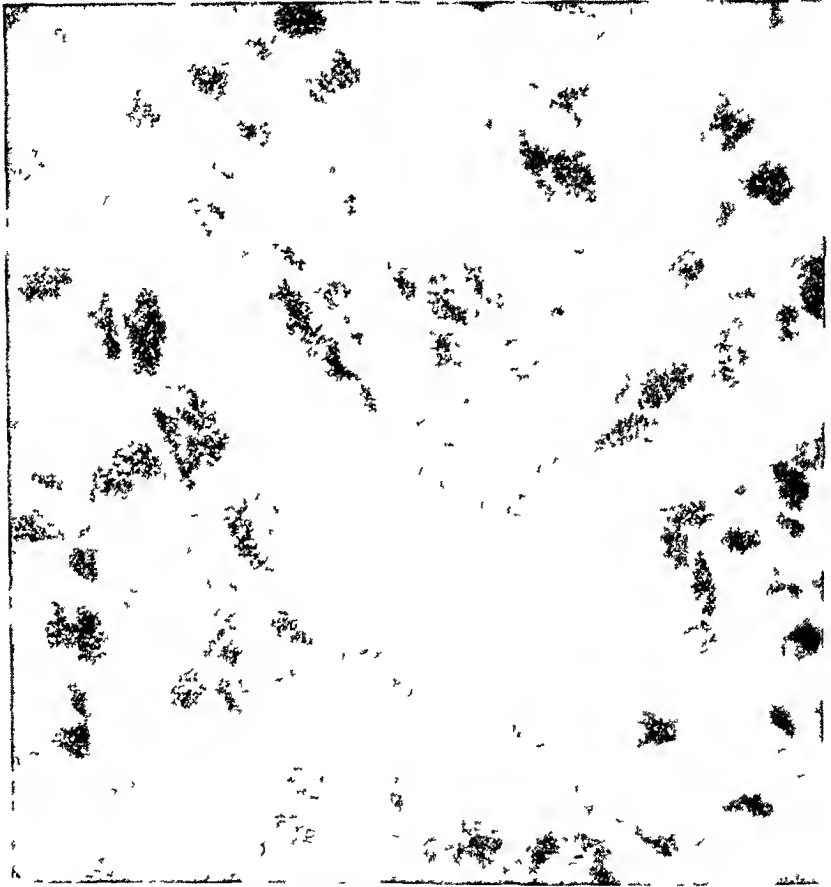


FIG. 6. Section of spleen. Hematoxylin and eosin stain. $\times 900$. In the center of the figure there is a sinusoid cut longitudinally and surrounded by the loose reticular network of the red pulp. The lining endothelium of the sinusoid is swollen and apparently in the process of desquamating into the lumen.

packed mononuclear cells many of which were in mitosis. No suggestion of reticulum formation could be made out here, and giant cells were relatively infrequent. These nodules showed evidence of rapid expansile growth in that they compressed the surrounding liver cords into a pseudo-capsule at their periphery. With Foot's reticular stain the argyrophyl fibers, which outlined the liver cords, extended lightly but fairly uniformly throughout the reticular areas. Occasionally their course coincided with the broad reticular fibers previously described, but it was impossible to demonstrate any definite connection between the cells and these fibers, although a few cells showed a fine precipitation of silver in their cytoplasm.

Spleen The capsule was not infiltrated or thickened. The normal architecture of the organ had disappeared. The white pulp of the Malpighian corpuscles was completely replaced by reticular hyperplasia which was essentially the same as described in the reticular areas of the liver. The sinusoids contained loosely packed mononuclear and giant cells with a minimal number of red blood cells. Their lining epithelial cells were sometimes normal but were often hyperplastic and definitely in the process of desquamating into the lumen (figure 6). Argyrophyl fibers, which were abundant in the blood vessel walls and in the fibrous framework of the organ, extended lightly and rather irregularly to all parts. The number of these fibers seemed to vary directly with the degree of reticular hyperplasia which was present in the different areas of the spleen.

Bone Marrow The rib marrow only was examined with hematoxylin and eosin stain. No myeloid tissue was present. The medulla of the bone contained adipose tissue, which was extensively infiltrated by large mononuclear cells, a few of which were in mitosis. No giant cells were present (figure 7).

Kidney There was very slight diffuse involvement of the interstitial tissues surrounding the tubules by mononuclear infiltration. This tissue also showed some evidence of hyperplasia by the presence of elongated spindle-shaped cells with vesicular

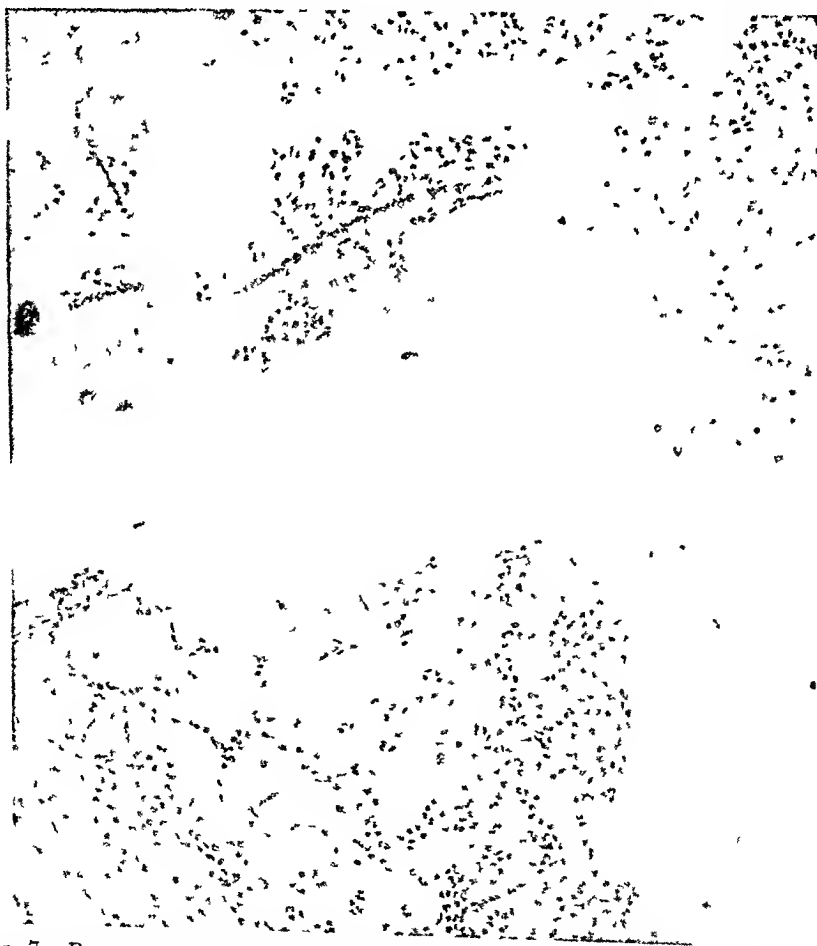


FIG 7 Bone marrow. Hematoxylin and eosin stain $\times 100$. This shows a complete absence of myeloid tissue and a loose infiltration of medullary fat by large mononuclear cells.

nuclei In addition to this there were areas of reticular hyperplasia with giant cells and mononuclear infiltration which displaced the surrounding tubules. In all glomeruli the cells lining the outer layer of Bowman's capsule were swollen.

Subcutaneous Nodules The microscopic appearance was identical with that of the nodule removed at biopsy.

Omentum, striated muscle, pancreas, and fragments of fibrous and adipose tissue attached to sections of other organs were remarkably free from cellular infiltration.

The free mononuclear cells which infiltrated the spaces of the reticulum varied greatly in size having a diameter of from one and a half to four times that of a small lymphocyte. Their essential structure seemed to be similar to that of the cells of the reticulum and the monoblasts of the peripheral blood. The abundant cytoplasm was sometimes dense and took the acid stain, but more often was basophilic and stained lightly. A striking feature of these cells was that they were highly phagocytic for coarse debris. The cytoplasm was often vacuolated. The structure of the nuclei varied greatly, they were round, oval, or deeply indented. They were usually vesicular with one nucleolus, but were sometimes hyperchromatic. In sections stained with Wright's Giemsa, and Bailey's granular stain these cells showed no specific granules. *Multi-nucleated giant cells* were present only in sections of the liver, spleen, and kidney, that is, only in the organs where reticular hyperplasia was found. They did not occur in the blastomatous nodules or in the bone marrow. Some cells contained two nuclei and were slightly larger than the mononuclears, from these there were all variations up to very large cells with 10 or 12 discrete nuclei. They occasionally were seen dividing by mitosis with a very complex chromatin pattern in the manner of pure tumor giant cells.

CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF MONOCYTIC LEUKEMIA

Forty-two cases of monocytic leukemia from the literature have been reviewed. This probably represents little more than half of the total number which have been observed. Analysis of these cases shows this type of leukemia to possess the following characteristics. It occurred only in the white race and was definitely more frequent in the male than in the female. The youngest patient was five years and the oldest 71 years of age. The majority were adults. The onset in many cases was associated with an infection, either general or localized. Ulcerative stomatitis was frequently observed. This was often accompanied by a cellulitis and was far more extensive than is usually found with other types of leukemia. A moderate degree of fever was often present but was not a constant finding. Enlargement of the liver and spleen was frequently observed and when it did occur was usually of moderate degree, often first appearing late in the course of the disease. The lymph nodes were sometimes moderately enlarged but there was often no demonstrable adenopathy. There was universally a moderate to severe anemia of the secondary type. Platelets were either normal or reduced in number. There was a leukocytosis which usually varied between 5,000 and 200,000. The highest count exceeded 400,000 and aleukemic and subleukemic counts often occurred. The characteristic feature of the blood pictures was a relative increase in monocytes, varying from 50 to 96 per cent, averaging about 70 per cent of the leukocytes. The

majority of monocytes were characteristically immature. In monocytic leukemia a shift to the left often occurs in the other series of leukocytes. Immature cells of the myeloid series are present in the blood of many cases which remain essentially monocytic in type throughout their course. Such cells may constitute as high as 26 per cent of the total leukocyte count. When they reach a considerable number, areas of myelopoiesis may appear in the diffuse reticulo-endothelial hyperplasia.⁷ A complete change of type from monocytic to myelogenous leukemia has been reported by Fontana⁸ and by Kracke⁹ (in a discussion of Foord's paper). Fontana also cites a case in which a change from myelogenous to monocytic leukemia was observed by Craciuneau and Calcalb. These are by no means the only instances in which change of type has been reported, but it is interesting to note that the change frequently follows a prolonged remission induced by radiation. The significance of these cases can not be evaluated until a greater number have been studied by uniform, modern, hematological technique. A shift toward immaturity in the lymphocytes, if present, is slight. The duration of the disease is usually from one to 10 months with a definite majority of the cases terminating in three months. Recently Doan and Wiscman¹⁰ have made a valuable contribution to the conception of monocytic leukemia as a third, distinct type of leukemia by reporting the first case of this disease to run a distinctly chronic course.

Monocytic leukemia is always accompanied by characteristic pathologic changes in the fixed tissues. These consist of a hyperplasia of the reticulo-endothelial cells and differ only in detail from that described in the organs in the present case except that involvement of the lymph nodes, which is absent here, often occurs. This picture is usually readily differentiated from the other forms of hyperplasia of this system of cells such as are associated with faulty lipid metabolism and with Hodgkin's disease. However, borderline cases do occur, and as has been pointed out by Marchal and Baigetot,¹¹ difficulty may be encountered in distinguishing monocytic leukemia from Hodgkin's disease on both clinical and pathological grounds. The same type of reticulo-endothelial hyperplasia which constitutes the pathological background for monocytic leukemia may occur and run a malignant course without any evidence of leukemia appearing in the peripheral blood.

Although monoblastomata in the diffuse connective tissues have not been described in connection with monocytic leukemia, Lasowsky¹² has reported an aleukemic case of malignant reticulo-endotheliosis with blastomatous nodules which may have been of this character.

Leukemic infiltration of the skin has been described in five cases^{1, 13, 14}

DISCUSSION

This case comes under the classification of leukosarcoma and presents an aleukemic and a leukemic phase. There was an unusually widespread frankly malignant hyperplasia of reticulo-endothelial cells and the peculiar

feature of the pathologic change was multiple recurring monoblastomata which were formed by localized hyperplasia of the histiocytes of the diffuse connective tissues. In the aleukemic phase these nodules constituted the only involvement of the reticulo-endothelial system, while in the leukemic phase they were accompanied by hyperplasia of the reticulo-endothelial cells of the stroma of the organs. Since their occurrence antedated by at least five months both the leukemic blood picture and the clinical evidence of reticulo-endothelial hyperplasia in the liver and spleen, the nodules could not be explained either as localized deposits of circulating monoblasts or as tissue metastases.

The terminal leukemia was of pure monocytic type. Repeated examinations of the blood showed the great majority of the leukocytes to be monoblasts. And except for one count where there were 9 per cent myeloblasts, immature cells of the other leukocytic series were practically absent. In the spleen and bone marrow lymphoid and myeloid tissue were replaced by an overwhelming reticulo-endotheliosis.

Compared with the other hematopoietic tissues monoblastic tissue varies greatly in character and is unusually widely distributed throughout the body, so it may be expected to produce a more complex disease syndrome. However, the course of events in the present case finds a close parallel in a disease of the lymphatic system—malignant lymphoblastoma with terminal lymphatic leukemia. In both there is a characteristic type of malignant blastoma whose spread is usually limited to the tissues in which it originates, and the possibility at least of a terminal leukemia which reflects the character of the cells forming the blastoma.

CONCLUSIONS

1. Review of the literature and the study of the present case tend to substantiate the view that the monocyte has a separate origin from other leukocytes and that monocytic leukemia is a distinct disease.

2. A variant of monocytic leukemia, malignant monoblastoma with a terminal blood picture of monocytic leukemia, is described for the first time.

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CLINICAL STUDIES IN ELECTROCARDIOGRAPHY

III PERSISTENT ABNORMAL LEAD IV FINDINGS IN SERIAL ELECTROCARDIOGRAMS, WITH NEGATIVE THREE ROUTINE LEADS, IN CORONARY THROMBOSIS *

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IN a previous publication¹ we presented a clinical evaluation of routine chest leads in cases of chronic coronary artery disease and acute coronary occlusion, with the findings in a series of 86 patients in whom, in addition to the three routine leads, a Lead IV tracing had been made. Of this series, 25 were normal controls, 40 were cases of chronic coronary artery disease and myocardial damage, 13 were cases of acute coronary thrombosis, and 8 were non-coronary cardiac cases. Of the 40 cases with myocardial damage due to chronic coronary artery disease, 25 showed positive findings in the three routine leads and a negative Lead IV, 12 showed positive findings in the three routine leads and a positive Lead IV, and three cases showed negative findings in the three routine leads and an abnormal Lead IV. Of the 13 cases of acute coronary thrombosis, four showed an abnormal Lead IV in the presence of negative findings in the three routine leads.

In order to determine whether or not there is persistence of abnormal findings in Lead IV, the four cases last mentioned were studied by serial electrocardiography and the findings were as follows:

CASE I

This patient, a man 53 years of age, became acutely ill August 23, 1932, with marked precordial pain radiating to the left shoulder and arm. There was no vomiting. He was seen at home on that day and an electrocardiogram was made at the bedside. It showed the T-wave inverted in Lead I, and diphasic in Lead II, in Lead III the complexes were inverted, suggestive of myocardial damage. Lead IV was not done at that time. A second electrocardiographic examination was made at the bedside next morning (figure 1, A), and showed T₁ diphasic, T₂ poor, T₃ slightly above the isoelectric line. Lead IV tracing was not made.

The patient was admitted to the hospital August 24, and physical examination revealed the following: a very feeble pulse, weak and rapid heart sounds, cold perspiration and other signs of peripheral circulatory failure. There was a pericardial friction rub. The blood pressure was systolic 120, diastolic 80. The abdomen was markedly distended. The patient remained in the hospital two months, during which time several electrocardiograms were made which showed no change.

November 5, 1932, the patient came to the office as an ambulatory case and electrocardiographic tracing at that time (figure 1, B) showed only an inverted T-wave in Leads I and II.

On December 16, 1932, another electrocardiographic examination was made in the office (figure 1, C) which showed that the inverted T-wave in Lead I had become upright, was unchanged in Lead II, and was poorly visualized in Lead III.

* Received for publication May 22, 1934

A, Aug 24, 1932

B, Nov 5, 1932

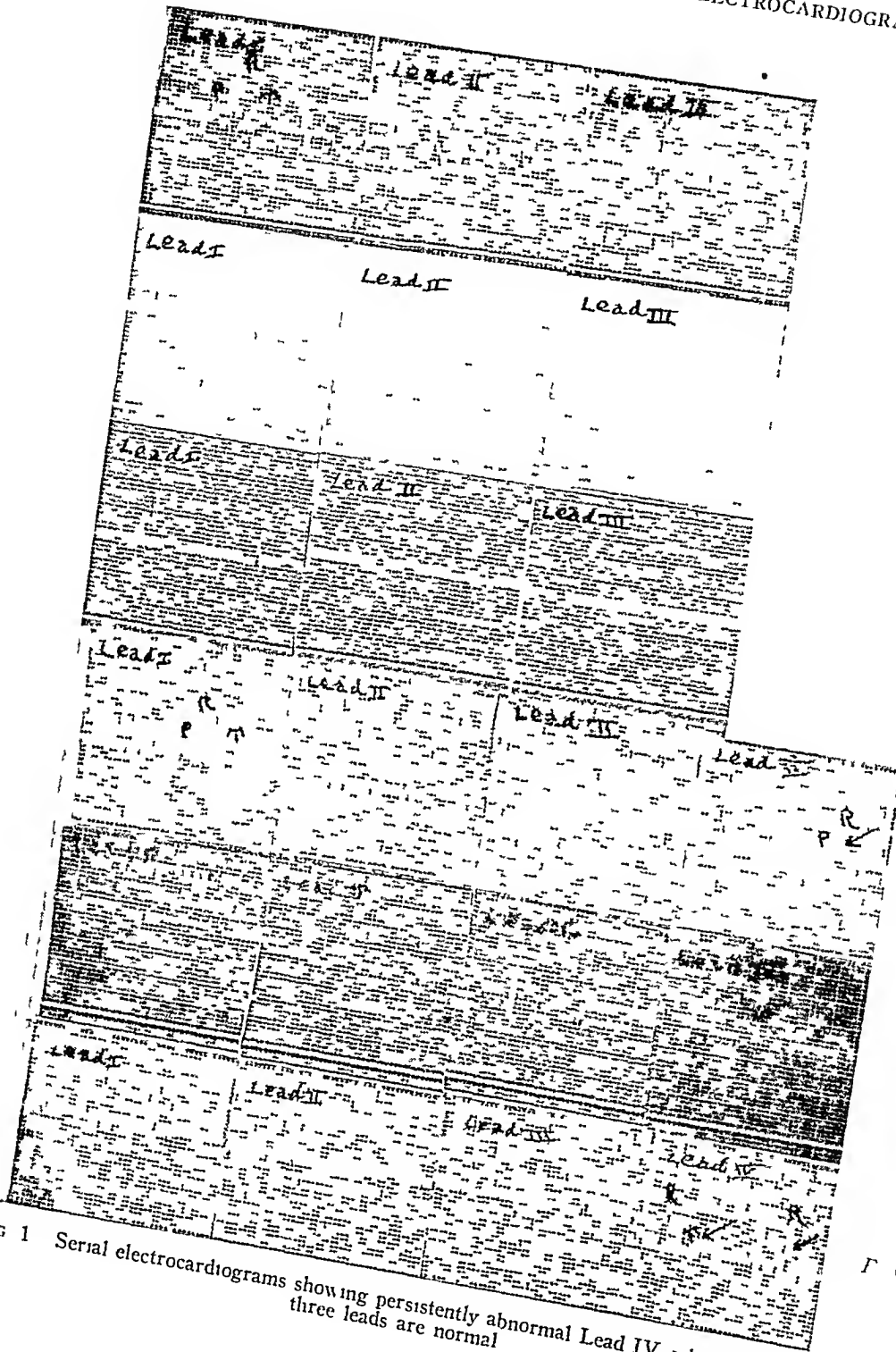
C, Dec 16, 1932

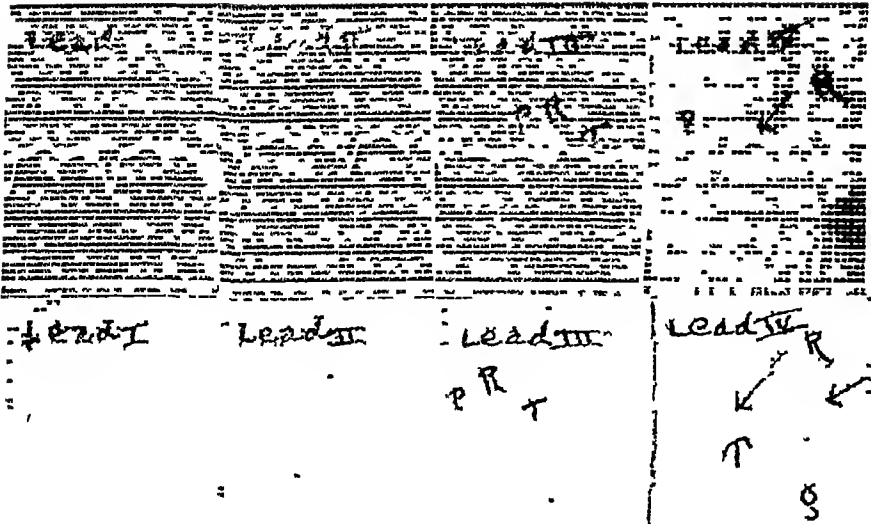
D Feb 13, 1933

E, June 8, 1933

F Oct 23, 1933

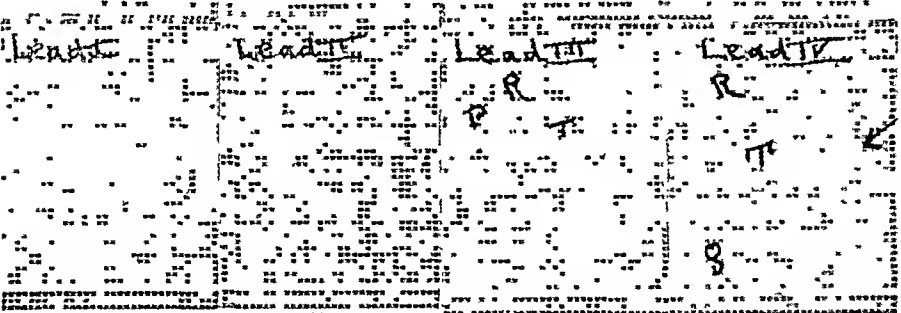
Fig 1 Serial electrocardiograms showing persistently abnormal Lead IV, while the routine three leads are normal





A, Jan 19, 193

B July 13, 193



C April 11, 193

FIG 3 Serial electrocardiograms showing persistently abnormal Lead IV, with the routine three leads suggestive of myocardial involvement

His heart was rapid but regular, with a gallop rhythm. The pulmonic second sound was accentuated. The blood pressure was systolic 150, diastolic 100.

January 19, 1933, an electrocardiogram (figure 3, A) was made at the office. The QRS complexes were widened in Leads I and II and there were diphasic T-waves in these leads. Lead III was normal. Lead IV confirmed the diagnosis of myocardial damage in that it presented a slurred QRS complex and a T-wave beginning above the isoelectric line.

July 13, 1933, the patient was still dyspneic, experiencing precordial pain on exertion. Physical examination revealed a gallop rhythm. The aortic second sound was accentuated. The blood pressure was 130 systolic and 90 diastolic. Fluoroscopic examination showed that the left border of the heart extended beyond the nipple line and that there was a widened aorta. Electrocardiographic tracing (figure 3, B) showed only one abnormality in the three routine leads, namely a diphasic T-wave in Leads I and II. Lead IV was persistently abnormal as at the previous examination.

April 11, 1934. The electrocardiographic findings (figure 3, C) were unchanged from the last examination. The original subjective complaints were still present.

CASE IV

While at work June 21, 1933, the patient, a man of 62 years, was suddenly seized with excruciating pain over the chest, radiating to the back and causing him to collapse. He was examined one hour later at Beth Israel Hospital, private service of Dr. I. W. Held, and was found to be in peripheral circulatory failure with clinical evidence of collapse. The heart sounds were faint and fetal in character, with a rate of 48. The blood pressure was 80 systolic and 50 diastolic. The abdomen was markedly distended. The liver was palpable. Electrocardiogram (figure 4, A) showed a normal Lead I, and cove T-waves in Leads II and III, evidence of right coronary thrombosis. Lead IV was not done.

On June 24, 1933, a second cardiographic tracing (figure 4, B) was made. Lead I was normal, the cove T_2 had become an inverted T_2 , and cove T_3 had become upright. Lead IV was abnormal in that there was an absence of the Q-wave and marked slurring of the QRS complexes. The patient was still very ill and the physical findings of the heart were unchanged from the previous examination.

On July 12, 1933, while still in the hospital, the patient developed severe pain over the splenic area which was diagnosed as perisplenitis due to splenic infarction. Electrocardiographic examination (figure 4, C) showed an unchanged Lead I, the T-wave less inverted in Leads II and III, and a persistently abnormal Lead IV, with the T-wave even more markedly downward directed.

On July 26, 1933, the patient, subjectively much improved, came to the office and another electrocardiographic tracing (figure 4, D) was made. It showed a normal Lead I, inverted T-wave in Leads II and III, and a persistence of the abnormal findings in Lead IV as at the previous examination. On August 28, 1933, the electrocardiographic findings (figure 4, E) were unchanged.

DISCUSSION

From the findings in the four cases reported above it is apparent that whereas the three routine leads returned to normal or almost to normal soon after the acute attack, Lead IV continued to show abnormalities, coinciding with the continuance of certain subjective symptoms in three of the cases. Without this persistence of the abnormal findings in Lead IV there would have been no electrocardiographic evidence of the fact that the patients'

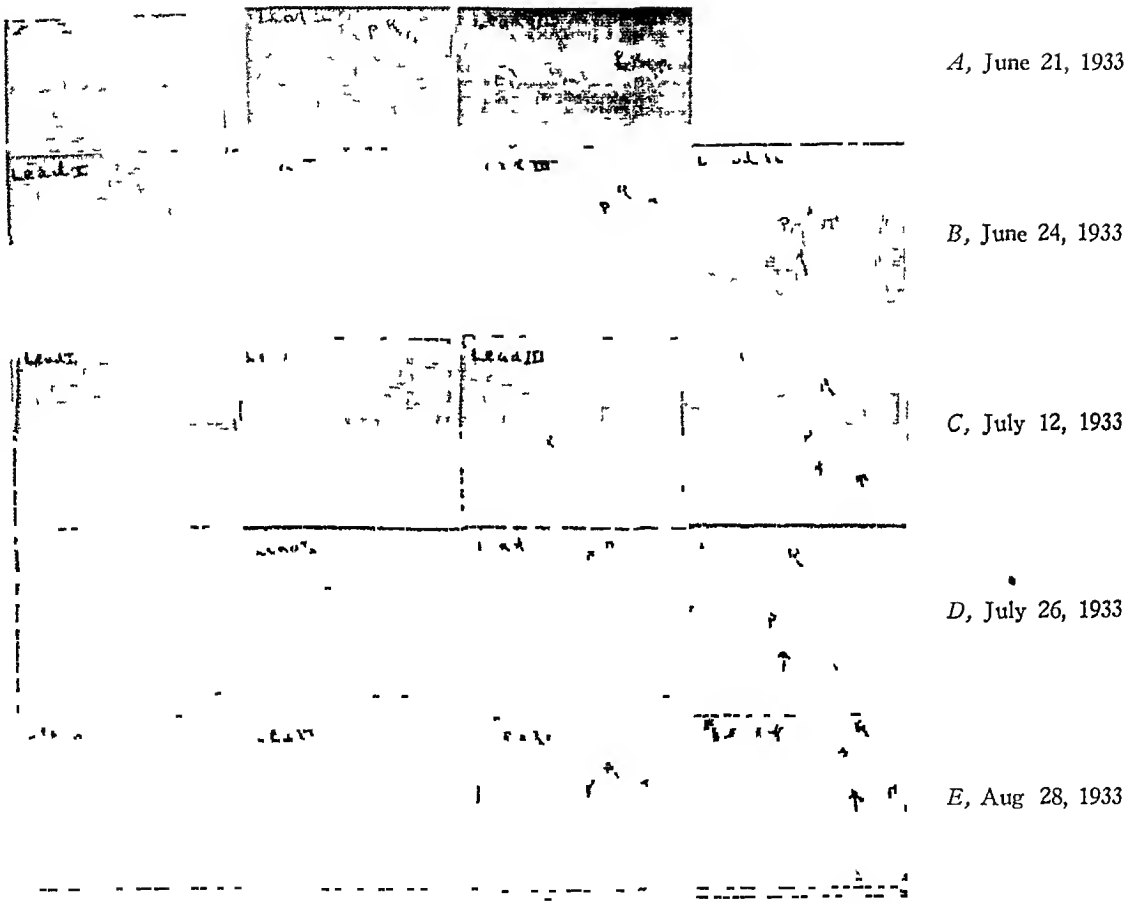


Fig 4 Serial electrocardiograms showing persistently abnormal Lead IV The routine three leads show evidence of myocardial damage

recovery from their myocardial damage was still incomplete. This is of particular importance because the management of these cases depends upon the degree of myocardial damage.

There is no valid explanation of the abnormality of Lead IV. There are authors who claim that an abnormal Lead IV has not as much diagnostic significance as have abnormalities in the three routine leads, but one may say, also, that abnormalities in the three routine leads are not always positive evidence of coronary occlusion, but may be due to myocardial damage secondary to hypertension, renal disease, or decompensated cor-pulmonum, as demonstrated by autopsy findings.²

It is possible that the abnormality of Lead IV is, also, not always indicative of coronary occlusion. We have seen this recently in a case on the service of Dr. M. A. Rothschild, which showed a persistently abnormal Lead IV which at autopsy proved to have been caused by circulatory failure as a result of thromboangitis of the smallest pulmonary vessels. The actual cause of the abnormality in Lead IV was probably anoxemia, as analysis of the patient's blood showed only 50 per cent of oxygen saturation. It has been shown experimentally by Keefer and Resnik³ and more recently by Rothschild and Kissin⁴ that anoxemia is a factor in producing the anginal syndrome. One must exercise caution therefore in interpreting abnormal Lead IV findings as directly due to coronary thrombosis with myocardial damage. In the four cases reported, the abnormal findings in Lead IV could not have been the result of anoxemia, however, for the reason that the serial electrocardiographic Lead IV tracings were not made in the acute stage, but after the subsidence of the acute attack. From the standpoint of prognosis, it is believed that further studies of the persistency of abnormal findings in Lead IV will provide criteria by which to judge expectancy of life.

SUMMARY

In order to determine the persistency of abnormal findings in Lead IV, four cases of coronary thrombosis were studied by serial electrocardiography, following the subsidence of the acute attack, and the findings reported. In two cases, the three routine leads returned to normal within a short period of time, in the remaining two cases, there was a modification of the early abnormalities in these leads, to a degree that they were no longer positively indicative of myocardial damage. In all four cases, the only abnormal electrocardiographic findings that have persisted, showing the incomplete recovery of the patients from their myocardial damage, are those in Lead IV.

CONCLUSIONS

Abnormal Lead IV findings persisted in four cases of coronary occlusion. This was not the case with the abnormalities in the three routine leads. Without the Lead IV serial tracings, therefore, one could not have been certain electrocardiographically that the patients were still not fully re-

covered from their myocardial damage. Hence we recommend that serial Lead IV tracings be made in cases of coronary thrombosis, not only for their diagnostic value but particularly to serve as a guide in treatment and management.

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CAROTID SINUS REFLEX HYPERSENSITIVITY *

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IT is not unusual to see patients who present symptoms of fainting, nausea, vomiting and convulsions without the presence on examination of any obvious pathological condition which might explain these attacks. The relation of disturbances of the function of the carotid sinus to the appearance of such symptoms has been not infrequently noted in the recent literature,^{1, 2} but our knowledge of the clinical phenomena in such cases is still fragmentary. It seems timely therefore to report certain observations made in two patients on the writers' service at the Kings County Hospital.

CASE REPORTS

Case 1 A 45 year old Italian laborer, admitted to the Kings County Hospital, complained that three hours prior to admission, on arising, for no apparent reason he suddenly developed dizziness, faintness, headache, vomiting, and a generalized convulsive seizure which recurred three times at 15 minute intervals. He then recovered consciousness and, except for a headache, felt perfectly well when brought to the hospital. His family history, as well as his past personal history, was negative. Physical examination showed a robust individual of medium height with no abnormal findings except carious teeth. The blood pressure was systolic 142, diastolic 84. The



FIG 1 Patient's normal electrocardiogram, Leads I, II and III. Rate 80. P-R interval, 0.12 sec. Lead III shows slurring of R and notching of P suggestive of some myocardial damage.

urine was normal. The blood chemistry examination showed urea, 29 mg per 100 cc of blood, creatinine, 1.2 mg, sugar, 133 mg. The blood count was: red blood cells, 3,850,000, hemoglobin, 70 per cent, white blood cells, 9,250, polymorphonuclear

* Received for publication September 22, 1934.

From the Medical Service, Kings County Hospital, Brooklyn, N Y.



FIG 2 Electrocardiogram during maintenance of pressure over right carotid sinus. Heart stopped completely at A and remained stopped for eight seconds except for one idioventricular beat at B

neutrophils, 78 per cent The blood and spinal fluid Wassermann examinations were negative A roentgen-ray of the skull showed no abnormalities

On careful reexamination of the patient, it was noted that the bulb of the right carotid sinus was more prominent than that of the left Figure 1 shows an electrocardiographic tracing of this patient in his normal condition Pressure on the right carotid sinus produced promptly a more and more marked slowing of the heart rate, until finally the heart stopped for eight seconds as shown in figure 2 The patient developed congestion of the face, the eyes turned upward and inward, the breathing became deeper and stertorous, profuse perspiration appeared, unconsciousness developed and in a few moments he suffered a generalized clonic convulsion Both subjectively and objectively the convulsive seizure seemed to be identical with the seizure at home Following this episode the patient complained of headache with nausea but recovered after one hour

Electrocardiographic studies of this reaction were made which showed a gradual slowing of the sinus rate with no evidence of any change in the auriculo-ventricular conduction time Cessation of cardiac pulsation for eight seconds took place, at the

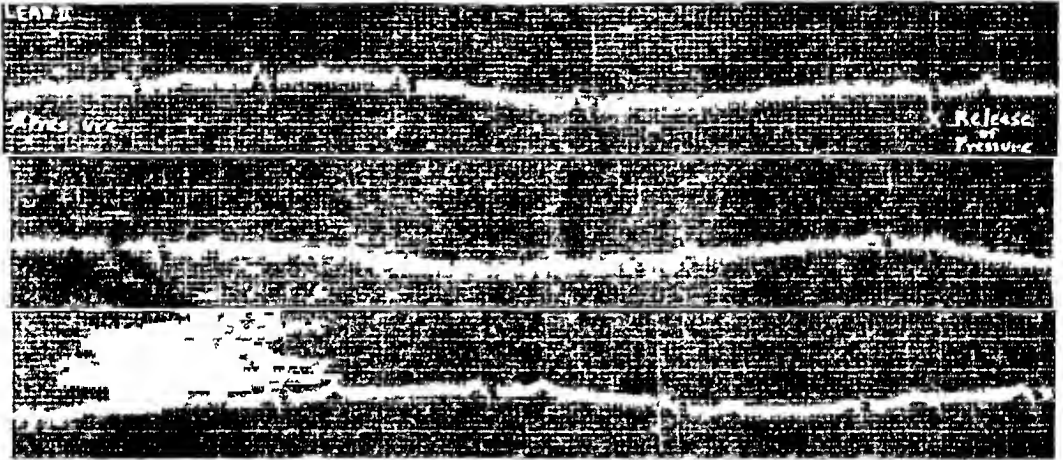


FIG 3 Electrocardiogram showing effect of pressure over right carotid sinus, pressure was released as soon as heart slowed

end of which time the patient had a convulsion The electrocardiogram showed one idioventricular beat at the end of three seconds In this first study, pressure was maintained until the patient had a convulsion In later studies, pressure was maintained only until the patient showed clinically signs of loss of consciousness Pressure was discontinued, however, before convulsions began A certain degree of quantitative correlation exists between the duration of the pressure and the intensity of the bodily response The removal of the pressure over the carotid sinus as soon as the heart rate decreased led to a slowing of the heart, followed by a return to the normal rate No cessation of the heart beat occurred This is shown in figure 3

Pressure on the left carotid sinus showed a definite slowing of the heart from 80 to 50 per minute, but no cessation of the heart beat Clinically the patient showed loss of consciousness exactly similar to that following pressure on the right carotid sinus with the heart effect as shown in figure 4

Pressure on the vagus below the carotid sinus gave no clinical or electrocardiographic changes (figure 5) Atropine sulphate, gr 1/50, was administered subcutaneously and pressure made over the carotid sinus 45 minutes after the administration of the drug Figure 6, which is an electrocardiographic tracing of the

atropine effect, shows that the heart rate, which had increased from 80 to 100 after the drug administration, dropped to 60 with pressure on the carotid sinus, but did not stop at any time. The patient, however, lost consciousness and appeared to be on the verge of a convulsion. In order to study the action of epinephrine, on the following day 15 minims of a 1:1000 solution were administered subcutaneously to the patient and electrocardiographic tracings taken 10 minutes later during pressure over the

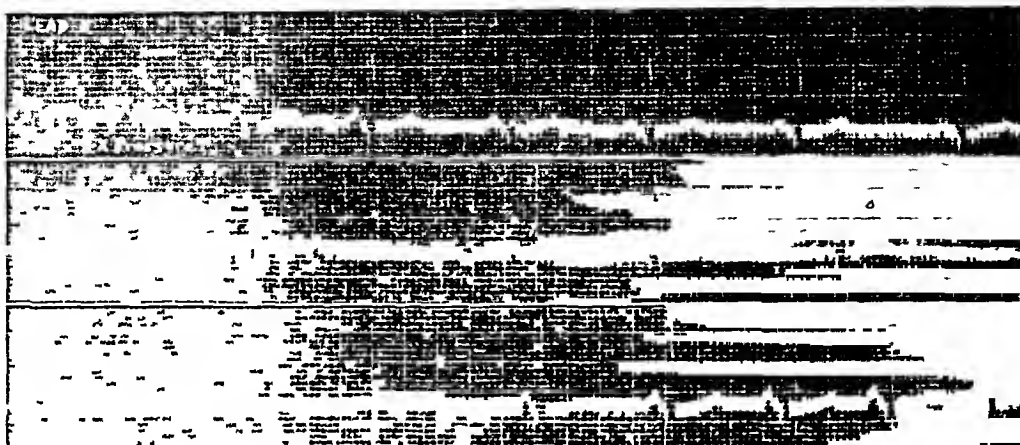


FIG 4 Electrocardiogram during maintenance of pressure on left carotid sinus

right carotid sinus. The heart rate slowed from 100 to 64 beats per minute but did not stop, as shown in figure 7. Clinically the patient developed dizziness but no loss of consciousness and no convulsions. Pressure over the sinuses of a series of 50 individuals in the wards suffering from a variety of other diseases failed in every case to show complete stoppage of the heart, loss of consciousness, or convulsions, although dizziness and a lowering of blood pressure were common.



FIG 5 Electrocardiogram during maintenance of pressure on vagus below carotid sinus, showing no electrocardiographic change

Case 2 Another example of this interesting condition occurred in a young married Jewish female, age 28 years, who reported attacks of faintness which were preceded by yawning, dizziness, headache, nausea but no vomiting, with a gradual increase in the severity of these symptoms for 15 to 30 minutes, until the patient lost



FIG 6 Electrocardiogram showing the effect of right carotid sinus pressure 45 minutes after administration of atropine 1/50 gr

consciousness for several seconds. Following this short period of unconsciousness there was a rapid return to a normal condition with the exception of a severe headache which usually persisted for several hours. These attacks occurred spontaneously, at irregular intervals, sometimes as often as twice a day, and at times did not return over a period of one or two months. There was no relationship of the occurrence of these attacks to the time of day, food, or physical activity. It was of interest to note that the first attack of this nature occurred during the fourth month of pregnancy.

Examination both during and between the attacks failed to disclose any of the



FIG 7 Electrocardiogram showing the effect of right carotid sinus pressure 10 minutes after administration of epinephrine

usual causes for this condition. Before unconsciousness occurred there was a marked pallor and frequent yawning spells with slow, deep inspirations. The pulse which was normally 76 beats, dropped gradually to six or eight beats per minute, and the blood pressure changed from 126 systolic and 80 diastolic to 60 systolic and 40 diastolic. A half hour after the patient regained consciousness the blood pressure and the pulse rate had returned to normal.

Pressure on the right carotid sinus reproduced the clinical picture observed in this patient during an attack. Pressure over the left carotid sinus gave a slowing of the pulse from 76 to 60, and a drop in blood pressure from 126 systolic and 80 diastolic to 108 systolic and 68 diastolic, but no subjective or objective changes in the clinical picture. The patient was given atropine sulphate, gr 1/100, three times a day, and has had no attacks for seven months.

Anatomically the carotid sinus consists of a fine network of nerves surrounding the beginning of the internal carotid artery, where it comes off as a branch of the common carotid artery. The carotid sinus nerve usually lies in the posterior part of the space between the internal and external carotids. There are two main branches, one going to the vagus, and the other through the glossopharyngeal nerve to the medulla. Clinically the carotid sinus is found just below the angle of the jaw at the upper level of the thyroid cartilage when the patient is lying on the back with the head elevated and slightly retracted. Occasionally the carotid sinus is situated somewhat higher or somewhat lower.

Parry³ (1799), Waller⁴ (1862), and Czermak⁵ (1866) showed that pressure over the area of the bifurcation of the carotid arteries in the neck caused slowing of the heart. They believed this to be due to direct vagus stimulation. This impression held sway for many years. In 1912 Sollman and Brown,⁶ experimentally in animals, showed that the vagus apparently did not play a direct part in this reaction since an isolated small piece of the internal carotid artery, 2 cm long, completely separated from all connections except those with the nerve plexus, gave a typical drop in blood pressure on being stretched and pulled but did not give this reaction after the connections

with the nerve plexus had been severed. Hering^{7,8} demonstrated conclusively that the slowing of the heart by digital pressure in the neck was not due to direct vagus stimulation but was the result of a reflex originating in a specialized portion of the internal carotid artery called the carotid sinus. This work was confirmed by Koch, Heymans, DeCastro, and others. Regniers, in 1930, showed that the slowing of the heart was due chiefly to a reflex action through the vagus but that there was also an inhibitory action of the carotid sinus on the tonus of the cardiac accelerator nerves. The drop in the blood pressure was due to the slowing of the heart and the inhibition of the vasomotor tonus. Schmidt⁹ showed that the respiratory center in the brain is influenced not only by the chemical changes in its blood supply but also reflexly by the carotid sinus. Cutting of the sinus resulted in the abolition of the normal response of the respiratory center to anoxemia. Stimulation of the carotid sinus reflexly stimulated the respiratory center.

Pressure on the carotid sinus also gives rise to gastrointestinal manifestations such as a feeling of epigastric uneasiness, nausea and vomiting. Danielopolu found that pressure on the carotid sinus first inhibited, then increased the activity of the intestinal peristaltic movements.

In individuals with a normal carotid sinus reflex, neither complete cessation of the heart beat on pressure, nor convulsions ever occur. Koch, Hess and Mehrman, Madelstamm and Lifschitz, and Soma Weiss and Baker¹⁰ have shown that the greatest reaction that can be obtained, even in patients who are somewhat more sensitive to pressure, as in the hypertensive or arteriosclerotic group, is a moderate slowing of the heart with a moderate drop in the blood pressure.

The cardiac arrest is due to two factors:

1. The temporary suppression of the sinus node, depriving the heart of the normal pacemaker.
2. The failure of the heart to form new foci of impulse initiation.

Persistence in pressure over the carotid sinus in a case, where complete stopping of the heart beat occurs temporarily, leads finally to the pacemaker breaking through the vagus depression with a resumption of the normal heart rate, or else to the development of a new focus usually in the ventricle which then acts as the focus for cardiac impulse initiation. The cerebral symptoms apparently are due to a vasomotor peripheral dilatation with the resultant cerebral anemia, accentuated by the slowing of the heart rate and a decrease in cardiac output with a slowing of the velocity of blood flow. Soma Weiss and Baker have shown that syncope and convulsions follow not so much as the result of the absolute degree of ischemia of the brain, as the rapidity with which this change occurs.

Whether the reflex in hypersensitive cases is the result of an abnormally sensitized state of the responsive organs with a normal carotid sinus, or a hypersensitive carotid sinus with normally responsive organs is not clearly known. Hyperactivity of the sinus is usually permanent but Weiss and Baker report two cases of recurrent hypersensitivity. The same observers

also report that local anesthesia of the sinus abolishes the ipsilateral reflex but not the contralateral reflex. In general it may be said that the hypersensitivity of the sinus is bilateral although usually the most marked effects are obtained by pressure over the right carotid sinus.

Electrocardiographic studies have shown that pressure on the carotid sinus is most frequently accompanied by an increasing A-V block, from prolonged P-R intervals to complete A-V block. This is often accompanied by ventricular extra-systoles. After the block develops, either ventricular nodal rhythm, ventricular extra-systoles, or bizarre complexes as seen in ventricular fibrillation, may occur. In our case, however, the usual findings were not present, there being at no time, from pressure over either the right or the left carotid sinus, any sign of an A-V block, either partial or complete.

Atropine paralyzes the parasympathetic or vagus nerve endings but does not affect the vasomotor reactions which take place through the sympathetic nervous system. In our case, atropine in adequate dosage removed all the vagus response except for a slight slowing which may be due to the effect of carotid stimulation in suppressing the cardiac accelerator nerves.

Epinephrine, through its property of stimulating the sympathetic nervous system, increasing the heart rate, increasing blood velocity and blood flow, stimulating the heart muscle directly, and stimulating the accelerator fibers of the heart, counteracts both the cerebral and the cardiac reactions. In our case, all reactions were abolished by epinephrine except for some slowing of the pulse, the vagus effect apparently being stronger than the epinephrine effect. Nathanson¹¹ has shown similar results. In addition he has also shown that ephedrine, calcium gluconate and caffeine have no effect, whereas digitalis acts to increase the cardiac effect of carotid sinus stimulation as the result of a summation effect on the A-V conduction system. Surgically, in those cases where there is a palpable mass pressing on the carotid sinus, removal of this mass will often relieve the condition. Weiss and Baker report one case where no mass could be found. The carotid nerve was cut with complete relief of the symptoms in this case. Medicinally atropine and epinephrine are the drugs of choice.

SUMMARY

- 1 Two cases are presented of carotid sinus hypersensitivity
- 2 Pressure on the right carotid sinus produced unconsciousness, convulsions, and cessation of the heart beat for eight seconds as shown by electrocardiogram
- 3 Atropine stops the cardiac effect of carotid pressure, but not the cerebral effects
- 4 Epinephrine counteracts both the vasomotor cerebral response and the cardiac response
- 5 The importance of this clinical picture must be kept in mind in studying cases of so-called idiopathic epilepsy or convulsions of unknown origin

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A CHEST ROENTGEN-RAY STUDY OF THE ADULT NEGRO POPULATION OF AN ENTIRE COMMUNITY

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WITH pulmonary tuberculosis in the United States reaching the point where many authorities predict its early relegation to the list of minor causes of death,¹ it has become essential to protect our present low mortality levels through the study and elimination of such reservoirs of infection as are recognized to be present among our heavily infected negro population. The literature clearly acknowledges that tuberculosis in the American negro with its high mortality rate is indeed an urgent problem. For many reasons the control factors which have proved so successful among our white population have found little application among the negroes. Sanatorium beds have not been provided at the same rate as for white patients. Educational facilities have been definitely less for the colored group. The economic standards of the colored race have not kept abreast of those of the white people and the consequent lower living conditions have favored undue exposures to infection and reinfection by tubercle bacilli. The presence of a notably high incidence of low grade constitutional infections among the negroes has rendered them more prone to the development of such diseases as tuberculosis. Our knowledge of inherent racial susceptibility to tuberculosis has been entirely conjectural.² Postmortem studies upon the lungs have been repeatedly made, however, and with the invariable finding of an undue incidence among the negroes of lesions of the exudative type, suggestive of a lack of the tendency to chronicity usually encountered in the white race.³ In how far these findings are due to exposure of the negro to unusually massive dosages of tubercle bacilli and to what extent racial lack of resistance determines the character of the lesions it is at present impossible to state.

Opie⁵ contends that there is relatively little known concerning tuberculosis as a manifest disease in the general colored population, i.e. morbidity from tuberculosis as distinguished from mortality, except by vague inference. No effort appears to have been made to determine how tuberculosis spreads among the negro group or what are the conditions which modify this spread. Yet, at Detroit, Chadwick⁶ succeeded in changing the trend from an increasing to a decreasing rate by the allotment of beds for colored patients to the hitherto unobtainable rate of 15 beds per annual death.

* Read before Mississippi Valley Sanatorium Association, September 28, 1934, Cedar Rapids, Iowa

Macon County, with a *total* census of 81,674, has a negro population of 1,947. Although a certain specified number of beds has never been set aside for their care, facilities for diagnosis and treatment have been available since 1923. The living standards of the negro population of Macon County are considerably better than in many other communities. During more favorable employment years there was little unemployment among them, and many were employed in industrial occupations at a fair living wage. In order to safeguard the present level of mortality from this disease (30.4 per 100,000, in 1933) and at the same time determine the actual morbidity of tuberculosis among the existing adult negro population, a roentgen-ray survey was conducted on a large scale. This method of examination was decided upon in conformity with existing opinion of phthisiologists that complete dependence may be had upon the roentgen-ray to find cases of early tuberculosis, and that all adults should be roentgen-rayed regardless of the findings of the physical examination.⁷ The type and extent of tuberculous lesions present are accurately revealed by the roentgenological examination, in the opinion of Rigler,⁸ and Sergent considers that "A radiological examination is an autopsy of the living."

Single chest films were made on 1,005 out of 1,232 adults, or a percentage of 81.6. All ages between 20 and 94 years were examined in the survey. The examinations were made in nearly equal proportion between the sexes. Through repeated canvassing efforts our survey yielded 89.3 per cent of examinations in that important age group 20 to 40 years. In the age group "over 60," 45.5 per cent were examined.

After completion of this roentgen-ray survey the cases showing evidence of tuberculosis were grouped as primary tuberculous infections (Ghon foci, lymph gland involvement), and manifest tuberculous disease, active and inactive (Chart 1). It was found that there was a surprising number of pulmonary lesions of non-tuberculous character. The incidence of abnormal cardiac silhouettes also appeared high (Chart 2). Out of an examined group of 1,005 negroes, 11 cases (1.1 per cent) of active manifest tuberculosis were revealed. Nine of these, or 82 per cent, were found in the age group 20 to 40. The active cases in the first age group were equally distributed between the three stages, minimal, moderate, and far advanced (Chart 3). Out of a total of 46 *inactive* cases, 38 showed fibro-calcareous infiltrations of the parenchyma, five pleural calcifications, and three healed miliary lesions. Evidences of primary infection as manifested by single or multiple Ghon foci and lymph node involvements, all of them showing calcium infiltration, totaled 277, or 27.6 per cent. Lesions of clinical importance of non-tuberculous etiology were found in 38 cases, or 3.8 per cent (Chart 4). They included 10 cases of pneumonokoniosis, seven of passive congestion, two of unresolved pneumonia, one of chronic interstitial pneumonia, seven of bilateral basal lesions, one of bronchiectasis, four of chronic serofibrinous pleuritis, one of fibroma, three of mediastinal tumors, one of atelectasis, and one of pulmonary syphilis (tentatively diagnosed).

CHART 1

A ROENTGEN-RAY STUDY OF THE ADULT
NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933-34
(SUMMARIZED)

| Ages | Sex | Number of Adult (Ages 20-94) 1933 Canvass | Examined (Roentgenograms) | | Diagnosis | | | | |
|----------|-----|---|---------------------------|------|-----------|----------|-------------|--------------|---------|
| | | | No | % | Active | Inactive | Infection * | Non The Pulm | Cardiac |
| 20-40 | M | 344 | 310 | 90 1 | 4 | 13 | 96 | 10 | 14 |
| | F | 388 | 343 | 88 4 | 5 | 5 | 91 | 7 | 24 |
| 40-60 | M | 205 | 159 | 77 6 | 1 | 12 | 40 | 11 | 47 |
| | F | 172 | 137 | 79 7 | 1 | 12 | 37 | 3 | 39 |
| Over 60 | M | 61 | 26 | 42 6 | 0 | 2 | 8 | 6 | 13 |
| | F | 62 | 30 | 48 4 | 0 | 2 | 5 | 1 | 17 |
| All ages | M | 610 | 495 | 81 1 | 5 | 27 | 144 | 27 | 74 |
| | F | 622 | 510 | 82 0 | 6 | 19 | 133 | 11 | 77 |
| Total | | 1232 | 1005 | 81 6 | 11 | 46 | 277 | 38 | 151 |

* As evidenced by healed Ghon foci (single or multiple) and calcified tracheo bronchial lymph nodes

CHART 2

A ROENTGEN-RAY STUDY OF THE ADULT
NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933-34
(CARDIAC SILHOUETTE FINDINGS)

| Ages | No Examined | Sex | Cardiac Lesions | | | | | | | Total |
|----------|-------------|-----|-----------------|----------|-------------|----------------------|----------------------|-----------------|------------------------|-------|
| | | | Aortitis | Aneurysm | Hypertrophy | Aortic Regurgitation | Mitral Regurgitation | Mitral Stenosis | Atherosclerotic Plaque | |
| 20-40 | 310 | M | 9 | 1 | 0 | 0 | 1 | 3 | 0 | 14 |
| | 343 | F | 13 | 1 | 4 | 0 | 3 | 3 | 0 | 24 |
| 40-60 | 159 | M | 37 | 6 | 2 | 2 | 0 | 0 | 0 | 47 |
| | 137 | F | 26 | 5 | 3 | 2 | 1 | 1 | 1 | 39 |
| Over 60 | 26 | M | 8 | 3 | 1 | 1 | 0 | 0 | 0 | 13 |
| | 30 | F | 9 | 2 | 2 | 2 | 0 | 0 | 2 | 17 |
| All ages | 495 | M | 54 | 10 | 3 | 3 | 1 | 3 | 0 | 74 |
| | 510 | F | 48 | 8 | 9 | 4 | 4 | 4 | 3 | 77 |
| Total | 1005 | | 102 | 18 | 12 | 7 | 5 | 7 | 3 | 151 |

CHART 3

A ROENTGEN-RAY STUDY OF THE ADULT
NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933-34
(TUBERCULOSIS FINDINGS—STATISTICAL)

| Ages | No Examined | Sex | Manifest Tuberculous | | | | | | | | Infection * | | | |
|---------|-------------|-----|----------------------|---------|----------|------------|----------------|------------|--------------|-------|-------------|-----------------|------------------|-------|
| | | | Active | | | | Inactive | | | | Ghon Focus | Multi Ghon Foci | Calc Lymph Nodes | Total |
| | | | Minimal | Mod Adv | Advanced | All Stages | Healed Miliary | Fibro Calc | Pleural Calc | Total | | | | |
| 20-40 | 310 | M | 1 | 2 | 1 | 4 | 2 | 9 | 2 | 13 | 60 | 17 | 19 | 96 |
| | 343 | F | 2 | 1 | 2 | 5 | 0 | 5 | 0 | 5 | 56 | 20 | 15 | 91 |
| 40-60 | 159 | M | 0 | 1 | 0 | 1 | 1 | 9 | 2 | 12 | 32 | 4 | 4 | 40 |
| | 137 | F | 1 | 0 | 0 | 1 | 0 | 11 | 1 | 12 | 25 | 4 | 8 | 37 |
| Over 60 | 26 | M | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 5 | 2 | 1 | 8 |
| | 30 | F | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 1 | 3 | 1 | 5 |
| Total | 1005 | | 4 | 4 | 3 | 11 | 3 | 38 | 5 | 46 | 179 | 50 | 48 | 277 |
| % | | | 04 | 04 | 03 | 11 | 03 | 38 | 05 | 46 | 177 | 50 | 48 | 276 |

CHART 4

A ROENTGEN-RAY STUDY OF THE ADULT
NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933-34
(NON TUBERCULOUS PULMONARY LESIONS—OF CLINICAL SIGNIFICANCE)

| Ages | No Examined | Sex | Non Tuberculous Pulmonary Lesions | | | | | | | | | | | |
|---------|-------------|-----|-----------------------------------|--------------------|------------------|------------------|---------------------|-----------------|------------------|-------------|-----------|--------------------|---------------|-------|
| | | | Pneu mono lesions | Passive Congestion | Unres Pneu monia | Chr Interst Pneu | Bilat Basal Lesions | Bronchiec tasts | Pleural Effusion | Syph this * | Fi brosis | Medi astinal Tumor | Atel- ectasis | Total |
| 20-40 | 310 | M | 2 | 1 | 1 | 1 | 2 | 0 | 2 | 0 | 0 | 0 | 1 | 10 |
| | 343 | F | 0 | 2 | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 2 | 0 | 7 |
| 40-60 | 159 | M | 6 | 1 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 11 |
| | 137 | F | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 3 |
| Over 60 | 26 | M | 2 | 2 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 6 |
| | 30 | F | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Total | 1005 | | 10 | 7 | 2 | 1 | 7 | 1 | 4 | 1 | 1 | 3 | 1 | 38 |
| % | | | 10 | 07 | 02 | 01 | 07 | 01 | 04 | 01 | 01 | 03 | 01 | 38 |

CHART 5

A ROENTGEN-RAY STUDY OF THE ADULT
NEGRO POPULATION, MACON COUNTY, ILLINOIS—1933-34
(MISCELLANEOUS FINDINGS—WITHOUT CLINICAL SIGNIFICANCE)

| Ages | No Examined | Sex | Non Clinical Abnormalities | | | | | | |
|---------|-------------|-----|---------------------------------|-----------------------|---------------|----------------------|--------------|-------------|-------|
| | | | Irregular or Elevated Diaphragm | Eventration Diaphragm | Cervical Ribs | Bullet in Chest Wall | Dextrocardia | Empyema Old | Total |
| 20-40 | 310 | M | 24 | 2 | 1 | 1 | 0 | 1 | 29 |
| | 343 | F | 26 | 1 | 2 | 0 | 1 | 0 | 30 |
| 40-60 | 159 | M | 18 | 2 | 0 | 0 | 0 | 1 | 21 |
| | 137 | F | 6 | 5 | 5 | 0 | 0 | 0 | 16 |
| Over 60 | 26 | M | 5 | 0 | 0 | 0 | 0 | 0 | 5 |
| | 30 | F | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Total | 1005 | | 80 | 10 | 8 | 1 | 1 | 2 | 102 |

Non-clinical abnormalities that were found, included 80 irregular, elevated, or eventrated diaphragms, eight cervical ribs, one bullet in chest wall, one dextrocardia, and two old empyemas (Chart 5). Among the cardiac lesions noted were 102 with important aortitis and 18 with aneurysm. One patient with aneurysm discovered on this survey, died from this cause one week following his examination.

A summary of our investigation of tuberculosis morbidity among the adult negroes discloses the following:

1 The incidence of untreated, unrecognized, non-tuberculous clinical disease is unduly high.

2 Under favorable environmental conditions the negro possesses a morbidity rate only slightly higher than that for the white.

3 In all age groups there is noted calcium deposition within the parenchymal and lung root fields which is present to a greater extent than among white people.

4 Among the discovered cases, the various stages of the disease were comparable in type to those seen in the white. In all but one instance the lesions were productive rather than exudative in type.

5 An important number of persons were found with bilateral apical, extensive fibrosis, indicative of a resistance to tuberculous infection not unlike that found in the white race.

6 The finding of a high percentage of healed primary infections, which through the years had resulted in no manifest parenchymal disease, appears significant of inherent resistance and not supportive of the older theory of racial susceptibility.

The impressions derived from this survey lead to the suggestion that tuberculosis in the negro may be controlled by the same methods that are being successfully employed for the white population inasmuch as the disease in the negro appears to be dependent upon the same factors of economy, infection, and environment. Many recent observations have served to confirm the fact that education, adequate provision of sanatorium beds and diagnostic facilities have served importantly to reduce the morbidity and mortality among this racial group.

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PLASMA CHOLESTEROL IN TUBERCULOSIS AND AMYLOID DISEASE *

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STUDIES of the cholesterol content of the blood in infectious diseases have shown that the acute febrile disorders,^{1,2,3,4} and the acute stages of syphilis,⁵ leprosy⁶ and tuberculosis^{3,7} are associated with hypocholesterolemia. In long standing tuberculosis, however, the blood cholesterol is not constant as in acute infections because the chronicity of the process entails complications which alter the level of the cholesterol in the blood. Variations in the blood cholesterol in phthisis are dependent on the severity of the tuberculous lesion, the body nutrition, and complications such as anemia and, as we expect to demonstrate, renal amyloidosis.

Bacmeister and Henes,³ and Henes⁴ found normal values for blood cholesterol in early tuberculosis, but an appreciable reduction was observed in advanced and fulminating cases associated with cachexia. Eichelberger and McCluskey⁷ noted hypocholesterolemia in severe cases running a downhill course, and conversely, a rise in cholesterol in cases with clinical improvement. They believed these changes indicated an association between cholesterol and the degree of resistance and immunity to tuberculosis. Rosenthal and Patrzek,⁸ Warnecke,⁹ Szule¹⁰ and Macchioro¹¹ observed a terminal drop in the blood cholesterol. Bonnamour and Pizzera¹² confirmed this tendency toward terminal hypocholesterolemia in tuberculosis but considered this phenomenon could scarcely yield any prognostic evidence not already shown by the clinical condition of the patient. Sayago and del Villar¹³ noted a gradual increase in the blood cholesterol in patients with tuberculosis for 45 days prior to death, this finding lacks confirmation. Chauffard, Richet and Grigaut¹⁴ observed a normal blood cholesterol in afebrile tuberculous patients, and a definite decrease in febrile cases. Monceaux¹⁵ made an unsuccessful attempt to correlate the cholesterol variations in blood with changes in the adrenal glands in tuberculosis. Sweany, Weathers and McCluskey¹⁶ suggested that cholesterol plays an active part in developing resistance to this disease, and von Babarczy¹⁷ observed hypocholesterolemia in cases with increased sensitivity to tuberculin. Levinson,¹⁸ however, could not find any evidence of increased resistance to tuberculosis in animals fed cholesterol.

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MATERIAL AND METHODS

Fasting blood specimens were collected in a group of 84 cases of severe tuberculosis. Determinations were made by the Sackett modification of the Bloor method¹⁹ using the modified procedure for colorimetric estimation employed in this laboratory²⁰. In some instances serial determinations were performed on the same patient. A few cases of osseous and peritoneal tuberculosis are included, although most of these patients suffered from advanced pulmonary tuberculosis with cavitation and clinical evidence of activity.

The cases studied were subdivided into five clinical groups with reference to the presence and degree of complicating amyloid disease. The Congo Red test, proteinuria, edema and renal function were the basis for the following classification:

Group I Tuberculosis without amyloid disease (negative Congo Red test)

Group II Tuberculosis with early amyloid disease not involving the kidneys (positive Congo Red test, no proteinuria)

Group III Tuberculosis with early amyloidosis of the kidney (positive Congo Red test, constant proteinuria)

Group IV Tuberculosis with amyloid nephrosis (positive Congo Red test, marked proteinuria, edema and other signs characteristic of nephrosis syndrome)

Group V Tuberculosis and amyloid contracted kidney (positive Congo Red test, marked proteinuria, signs of impaired renal function)

RESULTS

I Tuberculosis without Amyloid Disease There were 34 cases in this group. The predominating pulmonary lesion was ulcerative tuberculosis associated with a distinctly positive sputum and marked constitutional symptoms, two cases of bone and two of peritoneal tuberculosis were included in this series. The cases in table 1 are arranged according to the cholesterol level. Other data, such as age, extent of the tuberculous lesion and the duration, are tabulated, with a follow-up, six months after the cholesterol determination. The lowest cholesterol level occurred in one patient shortly before death in which only a trace was found (M. S.). The highest value was 286 mg per 100 c.c. of blood. There was no apparent correlation between the plasma cholesterol and the age, extent or duration of the disease.

A striking relation between the subsequent clinical progress of these patients and the cholesterol concentrations of the plasma is evident. In all 13 cases with a cholesterol concentration below 150 mg per 100 c.c., death followed within a brief period, generally within a month, often in a few days. In the other 21 cases with normal or slightly elevated cholesterol levels the six month mortality was 22 per cent. It is probable that a subsequent hypocholesterolemia may have occurred in the fatal cases, unfortunately serial cholesterol determinations were not made.

TABLE I
Plasma Cholesterol in Tuberculosis

| Case | Age yrs | Lesion * | Duration | Plasma Cholesterol mg per cent | Subsequent Course † |
|------|---------|-----------------------|----------|--------------------------------|--------------------------|
| D R | 12 | B C P | 1 year | 286 | Improved, left hospital |
| F M | 25 | Tb Hip ^a | 4 years | 280 | Unchanged |
| E B | 20 | B C P | 6 " | 240 | Unchanged |
| M R | 16 | B C P | 12 " | 207 | Died in 20 days |
| R M | 28 | Tb Perit ^a | 1 " | 203 | Unchanged |
| A H | 57 | B C P | 1 " | 196 | Unchanged |
| H Z | 61 | B C P | 8 " | 194 | Died in 18 days |
| C M | 23 | B C P | 1 " | 193 | Died in 5 months |
| H A | 47 | B C P | 2 " | 185 | Unchanged |
| A F | 28 | B C P | 2 " | 185 | Improved |
| H B | 50 | B C P | 3 " | 184 | Improved |
| W F | 40 | Potts ^a | 2 " | 183 | Died in 10 days |
| D U | 38 | B C P | 1 " | 183 | Died in 2 months |
| J V | 25 | U C P | 2 months | 182 | Improved |
| J S | 54 | B C P | 1 year | 181 | Died in 2 months |
| C S | 73 | B C P | 5 years | 178 | Left hospital in 4 mos |
| J G | 63 | B C P ^a | 10 " | 175 | Unchanged |
| J H | 60 | B C P | 6 " | 173 | Unchanged |
| C H | 62 | B C P | 5 " | 167 | Unchanged |
| G W | 54 | B C P | 1 " | 166 | Left hospital 1 mo later |
| F C | 28 | B C P | 2½ " | 159 | Improved |
| D H | 23 | B C P | ½ " | 147 | Died in 10 days |
| P H | 61 | Chr Pro | 5 " | 146 | Died in 19 days |
| F S | 24 | B C P | 2 " | 144 | Died in 11 days |
| M R | 25 | B C P | 5 " | 144 | Died in 23 days |
| H M | 39 | B C P | 4 " | 138 | Died in 22 days |
| L C | 40 | B C P | 8 " | 135 | Died in 36 days |
| K P | 33 | B C P | 4 " | 134 | Died in 3 days |
| P T | 40 | B C P | 4½ " | 122 | Died in 1 day |
| J B | 18 | B C P | 4 months | 118 | Died in 2 days |
| A H | 31 | Perit Tb ^a | 6 " | 111 | Died in 42 days |
| J W | 35 | B C P | 2 years | 108 | Died in 3 days |
| R A | 26 | B C P | 1 " | 105 | Died in 9 days |
| M S | 24 | B C P | 6 months | trace | Died in 2 days |

For explanation of symbols see footnote table 5

II *Tuberculosis and Early Amyloid Disease* This group is limited to seven cases. The diagnosis of amyloid was made by the Congo Red test and the lack of renal involvement by the absence of proteinuria.

The results shown in table 2 are essentially identical with those in table 1. Hypocholesterolemia in four cases was associated with an early fatal termination.

III *Tuberculosis with Early Amyloidosis of the Kidney* This group of cases had severe tuberculosis complicated by incipient renal amyloid degeneration. The amyloid involvement is recognized by a positive Congo Red test and a constant urinary protein. There were 16 cases of this type. Cholesterol values were higher in this group than in the previous ones studied. Only two cases with marked hypocholesterolemia were encountered, both of these terminated fatally within a brief period. The average

TABLE II
Plasma Cholesterol in Early Amyloid Disease

| Case | Age yrs | Lesion * | Duration years | Plasma Cholesterol mg per cent | Subsequent Course † |
|------|---------|----------|----------------|--------------------------------|---------------------|
| E M | 56 | B C P | 4 | 217 | Unchanged |
| J G | 28 | B C P | 3 | 193 | Unchanged |
| C M | 23 | B C P | 1 | 193 | Died in 5 months |
| G L | 42 | B C P | 2 | 188 | Unchanged |
| A P | 35 | B C P | 2 | 145 | Died in 1 month |
| A J | 20 | B C P | 1 | 133 | Died in 10 days |
| C S | 37 | U C P | 3 | 131 | Died in 16 days |

For explanation of symbols see footnote table 5

cholesterol value for the other cases was 228 mg per 100 c c. The six month mortality in those with normal or elevated plasma cholesterol was 22 per cent.

IV Tuberculosis with Amyloid Nephrosis and Edema Twenty patients of this type were studied. The outstanding clinical features of these cases were general anasarca and marked proteinuria. Pulmonary lesions were usually extensive and advanced. In three instances bone tuberculosis was present. Amyloidosis was recognized by the Congo Red test, and the nephrotic syndrome by the characteristic lipemia, the lowered blood proteins, the anasarca and the proteinuria.

A marked increase in plasma cholesterol, as high as 450 mg, was found, the lowest cholesterol observed at the time of edema was 200 mg. Fairly severe anemia (60 per cent hemoglobin or less) in four cases was associated with hypercholesterolemia.

When the prognosis was bad a tendency toward a falling plasma cholesterol concentration became evident, subnormal levels were noted at times. Seven cases with the nephrotic syndrome and plasma cholesterol levels of 200 mg or less, terminated fatally within two months, those with subnormal levels died within a month. In the 16 patients with an elevated plasma cholesterol the six month mortality was 45 per cent.

V Amyloid Contracted Kidney Seven instances of impaired renal function resulting from advanced amyloid of the kidneys were studied. Impaired renal function occurred with the nephrosis syndrome in four cases. Edema was absent in the three remaining cases. No direct relationship between nitrogen retention, impaired renal function and cholesterol was evident. A falling blood cholesterol was noted in several subjects shortly before exitus. Anemia and hypercholesterolemia were co-existent in three patients.

DISCUSSION

Anemia Subnormal blood cholesterol values have been reported in severe anemia particularly by Bloor and MacPherson²¹ and Muller and

TABLE III
Plasma Cholesterol in Early Amyloid of Kidney (No Edema)

| Case | Age yrs | Lesion * | Duration years | Plasma Cholesterol mg per cent | Subsequent Course † |
|------|---------|-----------------------------|----------------|--------------------------------|---------------------|
| M D | 32 | Potts ^a U C P | 6 | 333 | Unchanged |
| R F | 14 | B C P | 5 | 333 | Unchanged |
| D S | 17 | U C P | 5 | 330 | Died in 4 months |
| J M | 24 | U C P | 2 | 266 | Unchanged |
| L D | 30 | B C P | 4 | 224 | Unchanged |
| P A | 55 | B C P | 3 | 222 ^b | Died in 3 months |
| W M | 43 | B C P | 4 | 200 | Unchanged |
| M K | 24 | B C P | 10½ | 200 | Unchanged |
| S T | 45 | B C P | 4 | 200 ^b | Died in 2 months |
| A H | 57 | U C P | 4 | 196 | Unchanged |
| C I | 15 | Bone fbc ^a | 6 | 176 | Unchanged |
| W B | 20 | Potts ^a | 12 | 175 ^b | Unchanged |
| J G | 63 | B C P | 10 | 175 | Unchanged |
| J D | 38 | B C P | 3 | 172 | Unchanged |
| W G | 69 | B C P | 3 | 147 | Died in 2 months |
| M P | 48 | U C P | 7 | 127 ^b | *Died in 1 month |

For explanation of symbols see footnote table 5

TABLE IV
Plasma Cholesterol in Renal Amyloid (with Edema)

| Case | Age yrs | Lesion * | Duration years | Plasma Cholesterol mg per cent | Subsequent Course † |
|------|---------|--------------------|----------------|--------------------------------|--|
| N D | 22 | B C P | 4 | 407 | Living |
| M K | 25 | B C P | 3 | 340 | Died in 1 month |
| W B | 33 | B C P | 5 | 331 ^b | Left hospital (in extremis) after 3 months |
| E S | 46 | B C P | 4 | 300 | Living |
| R R | 27 | B C P | 6 | 290 | Living |
| J G | 21 | B C P | 3 | 290 | Living |
| V I | 17 | B C P | 2 | 284 | Living |
| S B | 21 | Potts ^a | 3 | 280 | Living |
| E H | 7 | Potts ^a | 1½ | 280 | Died in 1 month |
| E C | 39 | U C P | 2 | 265 | Living |
| A D | 39 | B C P | 2½ | 250 ^b | Died in 4 months |
| B K | 47 | B C P | 4 | 240 ^b | Living |
| M V | 20 | B C P | 1 | 212 ^b | Living |
| J B | 18 | B C P | 8 | 200 | Died in 1 month |
| K G | 22 | B C P | 2 | 200 | Died in 1 month |
| N P | 45 | B C P | 2 | 200 | Died in 3 months |
| M W | 29 | B C P | 2 | 177 | Died in 2 months |
| J D | 54 | B C P | 1 | 177 | Died in 3 months |
| D D | 15 | Potts ^a | 5 | 160 | Died in 1 month |
| W C | 53 | B C P | 3 | 160 | Died in 1 month |

For explanation of symbols see footnote table 5

TABLE V

Plasma Cholesterol in Amyloid with Impaired Kidney Function (Amyloid Contracted Kidney)

| Case | Age yrs | Lesion * | Duration years | Kidney Function | Plasma Cholesterol mg per cent | Subsequent Course † |
|-------|---------|--------------------|----------------|---|--------------------------------|---------------------|
| † F H | 49 | B C P | 3 | Terminal increase in N P N to 76 mg | 450 | Died in 4 months |
| † J D | 27 | B C P | 4 | Urea—N 36 mg , low urea clearance | 347 ^b | Died in 2 months |
| † J B | 45 | B C P | 4 | Sudden elevation in N P N to 90 mg , impaired 2 hour test | 258 ^b | Died in 4 months |
| † S W | 26 | Tbc osteo myelitis | 12 | N P N 110 mg | 234 ^b | Alive |
| W O | 28 | B C P | 4 | N P N 76 mg , impaired 2 hour test | 177 | Alive |
| M M | 47 | B C P | 4 | Terminal increase in N P N to 70 mg | 145 | Died in 2 months |
| S K | 32 | B C P | 5 | Increase in N P N to 63 mg , impaired 2 hour test, uremia | (194) § (127) § 97 | Died in 3 days |

^a Sputum negative Positive in all other cases^b Severe anemia (Hgb less than 60 per cent)

* Lesion B C P—bilateral caseous pneumonic tuberculosis, U C P—unilateral caseous pneumonic tuberculosis, Chr Pro—chronic productive tuberculosis, Perit Tb—peritoneal tuberculosis

† Subsequent course Clinical condition 6 months after cholesterol determination

‡ Edema present (nephrotic syndrome)

§ Previous determinations

Heath²² Since anemia often develops in a chronic debilitating disease, such as tuberculosis, this complication should be considered whenever hypocholesterolemia exists. The anemia did not appreciably affect the blood cholesterol in this series, on the contrary, in patients with proteinuria and edema an elevated plasma cholesterol was always found irrespective of the severity of the anemia. Cholesterol variations due to anemia in tuberculous affections complicated by amyloid, are of minor significance compared to the primary influence of inanition, cachexia and the abnormal lipid-protein metabolism of edematous renal disease.

Lipemia in Edematous Amyloid Nephritis A rise in the blood fats and cholesterol is characteristic of the edematous forms of Bright's disease known as "lipoid nephrosis" and the "nephrotic" type of glomerular nephritis. Such a nephritic lipemia is usually ascribed to an unusual mobilization of fat in the blood rather than to a defective absorption or oxidation of fat.²³ Fishberg²⁴ cites the experimental work of Boggs and Morris who induced lipemia and hypercholesterolemia in animals by repeated bleedings, he believes that this lipemia follows the diminution of the blood proteins

brought about by the loss of blood Fishberg²⁵ noted a direct relation between blood lipoids and the plasma proteins and considered the lipemia a compensatory process for the maintenance of normal osmotic pressure The results of Leiter²⁶ with plasmaphoresis and Shelburne and Egloff²⁷ with starvation fail to reveal any permanent or striking relation between blood proteins and cholesterol

The increased blood cholesterol in amyloid disease of the kidneys with edema is presumably identical with that of the edematous forms of nephritis It is noteworthy that hypercholesterolemia preceded the appearance of edema in cases of amyloid nephrosis with marked proteinuria

A high blood cholesterol is unusual in tuberculosis without amyloid In the absence of proteinuria, a normal or slightly elevated cholesterol level persistently maintained is a favorable prognostic sign Conversely, a low or falling cholesterol level in tuberculosis is a reliable indication of an early fatal termination Death occurred within several months, even within several weeks, in 14 cases having a plasma cholesterol level below 150 mg A prognosis judged by clinical signs was forecast less accurately than when the blood cholesterol was used as a guide

It is evident that in tuberculosis complicated by amyloid the proteinuria is the important factor depleting plasma proteins and resulting in lipemia Thus early amyloid without renal involvement (absent proteinuria) has no appreciable effect upon the blood cholesterol in tuberculosis The blood cholesterol rises before edema develops in cases of amyloid of the kidneys with marked proteinuria Hypercholesterolemia is most marked in cases of renal amyloid with edema (nephrosis syndrome) This is associated with the markedly diminished protein content of the blood which occurs in this condition as a result of the prolonged protein loss through the kidneys, cholesterol levels as high as 450 mg were observed

The elevated plasma cholesterol does not increase the resistance to the tuberculous process The fact that 45 per cent of the nephrotic group with elevated cholesterols terminated fatally within six months indicates this These clinical observations confirm the experimental results of Levinson previously cited In these cases there is a tendency towards a pre-mortal drop in plasma cholesterol Seven patients with blood cholesterol levels of 200 mg or less died within two months When the nephrosis syndrome is present a normal cholesterol level is an indication of a diminishing cholesterol curve and has the same significance as actual hypocholesterolemia

Epstein and Rothschild,²⁸ Schmidt,²⁹ Henes,³⁰ and Ashe and Bruger³¹ observed a drop of the blood cholesterol in terminal uremic states The cachexia incident to marked impairment of kidney function or to advanced tuberculous disease has the same depressing effect upon the level of the blood cholesterol

CONCLUSIONS

1 A maintained subnormal level of plasma cholesterol in tuberculosis is a serious prognostic sign signifying an early fatal termination

2 Renal amyloid disease with marked proteinuria is accompanied by a progressive increase in plasma cholesterol which precedes the development of clinical edema This hypercholesterolemia occurs even in the presence of severe anemia

3 The elevated plasma cholesterol in cases of renal amyloidosis does not appear to exert any protective influence against the underlying tuberculous infection

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ARTERIOSCLEROSIS IN DIABETES

I RELATIONSHIP BETWEEN PLASMA CHOLESTEROL AND ARTERIOSCLEROSIS II EFFECTS OF THE HIGH CARBOHYDRATE-LOW CALORIE DIET

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DEFINITION of age is difficult. Of the many available, the anatomical definition is, perhaps, the best. Gross¹ has clearly shown that, in embryonic life, the right side of the heart has a greater vascular tree than the left, and this relationship persists for some time after birth. As it assumes greater activity, however, the left ventricle becomes more and more richly supplied with blood, and with each succeeding decade, there is such an alteration of the vascular architecture that, at the seventh decade, the left-sided vasculature so overshadows that of the right as to point toward a relative right-sided anemia. As a protective mechanism against the possible obliteration of a large vessel, the patency of the arterie telae adiposae gradually increases. These vessels may eventually be capable of bearing the brunt of obliteration of even a main coronary artery. More recent studies also indicate the development of a vascular communication in the muscle of the heart. The findings thus suggest that, as age progresses, the chief danger is a relative right-sided anemia. The effect of the total change has been very succinctly summarized in the expression—A man is as old as his right coronary artery. This is a postmortem finding. Clinically, according to the electrocardiograph and also according to other postmortem data, it would now appear that the "artery of sudden death"—that which is most often affected by sclerotic changes, thrombosis, and embolism—is the anterior descending branch of the left coronary artery. Both findings, however, support the adage that "a man is as old as his arteries."

If alteration in vascular architecture is even approximately a characteristic of age, it would appear that the condition of the diabetic is now a happy one, the diabetic now lives long enough to enable the architecture to change. The high incidence of cardiovascular disease in diabetes mellitus has been commented upon repeatedly. Cardiovascular disease has replaced coma as one of the chief causes of death. There is, however, this disturbing difference: coma was the result of uncontrolled diabetes, whereas, cardiovascular disease, apparently, develops in spite of control, it develops whether the urine is, or is not, free of sugar and whether the blood sugar is or is not, normal. It is equally disturbing that it is not confined to elderly people and that only five years is the usual time necessary for its develop-

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ment, with diabetes of five years' duration, arteriosclerosis has developed regardless of the age, the frequent finding of calcification of arteries and other signs of arteriosclerosis in children is evidence of this fact

In a recent study of 500 carefully examined patients in our clinic² the incidence of cardiovascular disease was found to be 62.6 per cent. That the actual incidence is probably still greater is suggested from our experiences with a number of methods of examination when used singly and in combination with each other for the detection of vascular disease, and from a comparison of the *combined* method which we finally adopted, with careful postmortem studies. The combined method of examination shows the high incidence of cardiovascular disease among young diabetics. Thus, when grouped according to age (see table 1) 54.7 per cent of the

TABLE I
Incidences of Cardiovascular Disease among 500 Diabetics According to Age

| Age Period | Number | Cardiovascular Disease | |
|------------|--------|------------------------|----------|
| | | Number | Per Cent |
| -10 | 4 | | |
| 11-20 | 14 | 4 | 28.6 |
| 21-30 | 34 | 5 | 14.7 |
| 31-40 | 67 | 33 | 49.2 |
| 41-50 | 124 | 91 | 73.3* |
| 51-60 | 158 | 106 | 67.1 |
| 61-70 | 80 | 59 | 73.7 |
| 71-80 | 18 | 14 | 77.8 |
| 81+ | 1 | 1 | — |
| | 500 | 313 | 62.6 |

* Note. Among 243 individuals of 50 years of age and under, cardiovascular disease was found in 133—an incidence of 54.7 per cent.

patients of age 50 years and under had vascular disease, and for the same age-group, of 108 autopsies, Shields Warren³ found arteriosclerosis in 71 cases—an incidence of 65.7 per cent. Particular attention is drawn to the younger diabetics since, after 50 years of age, a high incidence of vascular disease is expected in all people, diabetic or nondiabetic.

The direct cause of the high incidence of vascular disease among diabetics is unknown. The contributing factors, however, appear to be many. Race and heredity operate in the diabetic as well as in the nondiabetic and, as stated previously, the duration of the diabetes is an important influencing factor. In the above mentioned investigation² we found that, with the disease of five years' duration or more, and regardless of the age of the individual and severity of the diabetes, over 80 per cent of our diabetics had cardiovascular disease. Thus (see table 2) of 144 diabetics who had the disease for five years or more, 121 were found to have arteriosclerosis, regardless of age—an incidence of 84 per cent, and of 81 individuals of age 50 years and under, but also with diabetes of five years or more, 69 had

TABLE II

Relationship between Cardiovascular Disease, Age and Duration of Diabetes among 500 Diabetics

| Period | Duration of Diabetes | | | | | |
|--------|----------------------|--------------------------|----------|---------------|------------------------|----------|
| | 5 Years and Over | | | Under 5 Years | | |
| | Total Number | Cardiovascular Disease * | | Total Number | Cardiovascular Disease | |
| | | Number | Per Cent | | Number | Per Cent |
| -10 | | | | 4 | | |
| 11-20 | 2 | 2 | 100 0 | 12 | 2 | 16 7 |
| 21-30 | 4 | 2 | 50 0 | 30 | 3 | 10 0 |
| 31-40 | 21 | 18 | 85 7 | 46 | 15 | 32 6 |
| 41-50 | 54 | 47 | 87 0 | 70 | 44 | 62 8 |
| 51-60 | 50 | 43 | 86 0 | 108 | 63 | 58 3 |
| 61-70 | 12 | 8 | 66 7 | 68 | 51 | 75 0 |
| 71-80 | 1 | 1 | 100 0 | 17 | 14 | 82 3 |
| 81+ | | | | 1 | 1 | 100 0 |

* Note Of 81 diabetics of age 50 years and under, 69 had arteriosclerosis—an incidence of 85 1 per cent

Of 144 diabetics of all ages combined, 121 had arteriosclerosis—an incidence of 84 0 per cent

signs of vascular disease—an incidence of 85 1 per cent The discovery of this high incidence of cardiovascular disease with the diabetes of five years' duration or more was due, as we have shown, to our combined method of examination, and that it very closely approximates the truth is suggested from postmortem findings, in his monograph on the pathology of diabetes mellitus, Shields Warren³ who has made a special study of diabetes, states "I have yet to see at autopsy a diabetic, or to read a protocol of a diabetic, whose disease has lasted 5 years or more, free from arteriosclerosis, regardless of age" Fortunately, however, as I believe the data to be presented here suggest, cardiovascular disease, in the young diabetic at least, is not inevitable The diabetic, as well as the nondiabetic, must die eventually *Premature* development of arteriosclerosis, however, appears to be a preventable condition, the data clearly indicate that the condition can, at least, be delayed

That the high incidence of cardiovascular disease noted in the past may have been due, to some extent, to the methods of treating diabetes, has been suspected for some time I am referring particularly to treatment with diets of low carbohydrate and high fat content Shepardson⁴ in a study of arteriosclerosis in young diabetics, observed "a striking parallelism between the reduction in average values of blood cholesterol and the reduction in the incidence of arteriosclerosis" Joslin has had the impression for some time that excess fat in the diet may be a factor in the premature development of arteriosclerosis⁵ and that, in his clinic, arteriosclerosis is decreasing

with the more liberal use of carbohydrates In a letter to me, Dr Joslin writes "since the use of 100 grams or more of carbohydrate with my diabetic patients, I believe the development of arteriosclerosis has been postponed It is difficult to prove this statistically because now patients live so much longer than formerly, that even without diabetes many would be showing arteriosclerosis With children there is definitely less arteriosclerosis than formerly" These impressions fit in with the fairly well established fact that continual feeding of large quantities of fatty substances and of cholesterol leads (at least in herbivora) to deposition of fatty materials in the intima⁶ and, it should here be observed, that lipid infiltration of the intima is the outstanding vascular lesion in the young diabetic

That excess cholesterol in the blood, if not the direct agent, may at least be an important contributing factor in the production of arteriosclerosis in the diabetic has been suggested repeatedly In their "Quantitative Clinical Chemistry," Peters and Van Slyke⁷ state that "there is little or no evidence to support such a theory Hypercholesterolemia is not observed with any regularity in arteriosclerosis" As I shall presently show, however, this observation is not in accord with a number of known facts

There is, firstly, the evidence of the pathologist I have referred to lipid infiltration of the intima This is a characteristic of the atheromatous type of vascular disease—the type which is very common in diabetics, and vascular disease in diabetes is largely confined to the intima, regardless of its site—heart, extremities, etc There is also the observation of Klotz and Manning⁸ concerning the association of fatty deposition in the intima with definite age periods, it is very frequent between age 20 and 30 years and unusual before age 10 and after age 50 years Thus, it should be noted, fits in with the previously mentioned high incidence of vascular disease in the diabetics of age 50 years and under Aschoff⁹ attributed the atheromatosis of diabetes mellitus to deposition of lipid materials in the arteries The lipoids, according to Aschoff, may not be the direct cause of the atheromatous changes, but they can influence the course of the disease by determining the degree of fatty infiltration of the hyalinized ground substance Shields Warren³ put it this way "The lipoids are not the first wave of the assault They are the reinforcements that consolidate the gains made by the attacking force The normal intima is not disturbed by fat but given an abnormal intima, atheromata will develop in proportion to the amount of fatty substances present" Labbé and Heitz¹⁰ believe that obliteration of the arteries in diabetes mellitus is due to localization of cholesterol in the intima

There is the evidence of chemical pathology Windaus¹¹ compared cholesterol contents of normal with diseased aortae and found the diseased vessels contained at least six to seven times as much free cholesterol as the normal and between 20 to 26 times as much cholesterol esters Selig¹² found between 3 and 4 per cent ether-soluble matter in normal aortae, whereas, atheromatous aortae yielded up to about 15 per cent of

fatty substances In three atheromatous vessels, Ameseder¹³ found that, of the "total fat," a very large portion—28.56 per cent—was unsaponifiable matter, chiefly cholesterol The high cholesterol content in atheromatous aortae has been confirmed by other workers^{14, 15} The case reported recently by Cullinan and Graham¹⁶ is probably the most striking example of this condition A young male, who had diabetes eight and one-half years, died of *coronary thrombosis* at the age of 27 years This, as the authors pointed out, appears to be the first case with such widespread arterial degeneration and death from coronary thrombosis at such an early age The cholesterol content of the dried aorta was 5.8 per cent, whereas, the aorta of a young nondiabetic female of about the same age (30 years) contained only 0.64 per cent These authors also record the finding of 10.4 per cent cholesterol in the dried aorta of a male, aged 66 years, with advanced atheroma

In addition to the observations on pathology and pathological chemistry, there is the chemistry of the blood Hypercholesterolemia is a common metabolic finding in diabetes mellitus Earlier analyses,^{17, 18} however, failed to reveal any characteristic abnormalities in the blood lipoids in patients with arteriosclerosis In 1925, Pribram and Klein¹⁹ found an increase of blood cholesterol in this condition, and, in the same year, Labbe and Heitz¹⁰ reported the finding of hypercholesterolemia in a case of endarteritis obliterans in a diabetic Mjassnikow²⁰ found it regularly in advanced arteriosclerosis of the aorta and coronary arteries In 1927, I reported findings in 16 cases of gangrene, the average cholesterol content of the blood plasma was 0.344 per cent and only one of these diabetics had a cholesterol of less than 0.200 per cent²¹ In 1929, I pointed out the high incidence of vascular disease among our patients with excess quantities of cholesterol in the blood²² In their earlier studies, Joslin²³ and Hunt²⁴ failed to find a relationship between circulating blood cholesterol and arteriosclerosis among diabetics However, this is not in conformity with later reports from the same clinic, according to White and Hunt²⁵ arteriosclerosis in the vessels of the legs was discovered by roentgen-ray in nine of 48 children in whom examinations were made, and hypercholesterolemia was found in 46 per cent of the cases studied The average cholesterol of all analyses preceding, coincident with, and following the discovery of the arteriosclerosis in the 9 children was 0.263 per cent In his recent address on "Fat and the Diabetic" Joslin²⁶ summarizes his experiences with children thus: Cataract and arteriosclerosis were many times more common among children with hypercholesterolemia than with normal cholesterol, nine of eleven children had high cholesterol values prior to the discovery of the arteriosclerosis, and in the subsequent courses of 67 children with high cholesterol, arteriosclerosis developed in 15 per cent, cataract in 8 per cent and nephritis in 6 per cent In the same address, Joslin also quotes Bloor as having found "higher values for cholesterol in the arteriosclerotic diabetic than in those without sclerosis" The finding of hypercholesterolemia with cataract is of interest, in view of the previous observation by O'Brien and Myers²⁷ that blood cholesterol was

found elevated in 54 per cent of cases of senile cataract. It would thus appear that my earlier findings have been amply confirmed.

The finding of normal quantities of cholesterol in cases of advanced arteriosclerosis, particularly of the atheromatous type, does not appear to fit in with a causal relationship between this blood lipid and vascular disease. This, however, in my opinion, does not *disprove* such relationship. The finding of a normal amount of cholesterol in the blood does not necessarily imply that the cholesterol is harmless. Whether cholesterol does, or does not, deposit in the intima, may depend largely upon its physical state. Bloor's observation²⁸ is of interest here. "*Deposition of cholesterol and its esters does not necessarily require a high cholesterol, but depends upon the ability of the blood to keep in solution a substance which is probably in a state of supersaturation*."

Interpretation of the above data is, however, not simple. As Shields Warren³ has pointed out, mere association of high cholesterol with arteriosclerosis is not enough. Otherwise, every time we eat a fat-rich meal, particularly eggs,* a bit of arteriosclerosis would be added. Causal relationship is, however, suggested from a variety of other data, particularly the results of experiment.

Since 1908, when Ignatowski produced arteriosclerosis by feeding rabbits with protein, much has been done with respect to experimental production of arteriosclerosis, and it was in 1912 when Anitschkow, in Leningrad, produced typical atherosclerosis in rabbits by the administration of pure cholesterol in olive oil. This was an important advance, since cholesterol atherosclerosis resembles very closely the atherosclerosis of man. For an excellent review of this subject, the reader is referred to the recent publication on arteriosclerosis by the Josiah Macy Jr. Foundation²⁹. In addition to these data, there is the recent work of Leary†³⁰ namely, the production of coronary atherosclerosis in rabbits comparable with the lesions found in man. What may prove to be of therapeutic value and also supports the view that the relationship between arteriosclerosis and blood cholesterol is causal and not accidental are the findings of Turner³¹ and of Turner and Khayat³². These workers found that administration of thyroid gland simultaneously with cholesterol prevented atheromatous changes produced by the latter in 17 of 19 animals, potassium iodide also exerted a strong protective action, thyroidectomy in itself did not cause a rise of blood cholesterol or lead to atherosclerosis. Potassium iodide failed to exert a protective action when the thyroid gland was removed. In these experiments a relationship was found between the level of circulating cholesterol and the development of atherosclerosis.

* A large egg contains about 0.4 gram of cholesterol.

† Leary points out that man is apparently the only animal that dies in life from coronary disease and almost universally acquires atherosclerosis in later life. It is also of interest here to note that, compared with nondiabetics of similar age, the incidence of coronary disease in diabetes is high. In 270 postmortem examinations, Shields Warren³ found coronary sclerosis in 124 cases—an incidence of about 46 per cent.

The problem of cholesterol and arteriosclerosis is obviously a very difficult one and is further complicated by the fact that so little is known of cholesterol itself. This applies both to its chemistry and physiology. Strictly, cholesterol is not even a fat. Though it is classified as a lipid, it is included among the latter group of substances largely because of its physical properties (solubility, etc.). As found in the body, it is probably not even a chemical individual. There is much to support the view that so-called cholesterol consists of two or more sterols differing in melting point, power to absorb ultra-violet light, precipitability and other properties. As stated, little is also known of its functions in the body, but that it is an essential constituent of protoplasm is suggested from its widespread distribution in nature.³³ As Bills³⁴ put it in his recent review of the physiology of the sterols, cholesterol occurs in the most diverse phyla of the animal kingdom, and if one can reason from the general to the specific, it would appear to be absent in no metazoa except the sponges and certain mollusks, and in these to be represented by one or another of the allied spongosterols or ostreasterols.

How excess cholesterol might lead to arteriosclerosis is not clear. Some time ago, from data I obtained on the colloidal osmotic pressure of the blood in diabetes mellitus,³⁵ I suggested increase of colloidal osmotic pressure in the capillaries as a possible cause. Though there was little direct evidence, the sum of all data (clinical and laboratory) then available tended to support the view that, in diabetics with hypercholesterolemia, an osmotic pressure greater than normal is constantly exerted in the capillaries. To overcome the latter, for purposes of renal excretion, a greater hydrostatic pressure is required, this increased pressure, though relatively small, when continued over a long period of time might have the same effect as more marked intracapillary pressure exerted over a short period of time. In animals, the latter when produced either by injection of epinephrine or by sympathetic stimulation, is alleged to cause arteriosclerosis. It is difficult, however, to reconcile this view with cases of arteriosclerosis without increase of blood pressure, and it is this type of arteriosclerosis which is common among diabetics, particularly in the younger age groups. More recently, I suggested hypervitaminosis as another possible cause.³⁶ This view was based upon a variety of data, namely, (*a*) the known action of irradiated ergosterol, (*b*) the intimate association of ergosterol with cholesterol, (*c*) the cholesterol content of the normal skin, (*d*) the high sterol content of the diabetic skin and, lastly, (*e*) the action of solar rays and artificial radiation on the skin. Combining these observations, it appears reasonable that the tissues of the diabetic with hypercholesterolemia are being bombarded continuously with excess quantities of irradiated ergosterol and thus are exposed to excess calcification. The high incidence of arteriosclerosis in diabetes with xanthosis^{37,38} is very suggestive. Hess, Weinstock and Helman³⁹ have suggested that the relatively high concentration of sterols in the skin and subcutaneous tissues is a provision for the more

direct exposure of the contained ergosterol to the activating light rays of the sun. Opposed, however, to hypervitaminosis is a characteristic of vitamin D, namely, the wide range between its ordinary therapeutic dose and that which is capable of producing vascular changes. Also, there is the fact that calcification of the arteries due to excess exposure to vitamin D centers largely about the media, whereas, the dominant vascular disturbance in diabetes is, as stated, in the intima. A number of factors may, however, operate together. Thus, combining their experience with cholesterol in hyperthyroidism and hypothyroidism with the observations by Aub, Bauer, Heath and Ropes⁴⁰ on calcium excretion in the same conditions, Mason, Hunt and Hurxthal⁴¹ have suggested that arteriosclerosis in the diabetic may be due to a combination of excess cholesterol and diminished excretion of calcium.

RESULTS OF A STATISTICAL STUDY OF THE RELATIONSHIP BETWEEN BLOOD CHOLESTEROL AND CARDIOVASCULAR DISEASE

Before attempting to relate blood cholesterol to arteriosclerosis, it is necessary to consider conditions other than arteriosclerosis which may influence blood cholesterol. As will presently be shown, though the finding of hypercholesterolemia may suggest a causal relationship between arteriosclerosis and blood cholesterol, normal quantities of cholesterol do not necessarily exclude such relationship. A possibility which must be considered is that, in such a case, the individual may have had excess quantities of cholesterol in the blood for some time and thus have developed arteriosclerosis, but, at the time of examination, there may have been some condition which lowered the concentration of this blood lipid.

To the end of 1933, we have made 5151 observations on plasma cholesterol among our diabetics. In practically all of the cases, the blood samples were collected under the same conditions with respect to preparation of patients, with extremely few exceptions, all bloods were collected in the fasting state. The purpose of this routine is to eliminate one important variable in the interpretation of cholesterol data, namely, the influence of food. It should here be observed that the cholesterol content of the blood may be appreciably affected by quantity and kind of food. As a rule, it is increased, the increase depending to some extent upon the type of food taken⁴² though it is not necessarily due to the cholesterol content of the food. At times, there may be no increase in the total blood cholesterol content, but an *alteration of the ratio of free cholesterol to cholesterol esters*⁴³. This, as will presently be shown, is an important consideration, in view of the method used for the estimation of blood cholesterol.

Though all blood samples were collected in the fasting state, the conditions were not strictly basal, bed patients only were at rest. Exercise is known to increase blood fat⁴⁴. However, the amount of exercise must be quite appreciable and in general though exercise may increase the fat content of the blood, there is generally little or no change in cholesterol⁴⁵.

The method we use routinely, and by means of which the data in this investigation were obtained, is based upon a reaction which is affected by free cholesterol as well as its esters, namely, the Liebermann-Burchard reaction. The test thus reflects the *total* concentration of cholesterol in the blood. It does not, however, entirely eliminate all possibility of error. The Liebermann-Burchard reaction is a color reaction and the amount of color developed depends not only upon the total amount of cholesterol, but on the proportions of free cholesterol and cholesterol esters, it appears to be greater with the esters than with a corresponding amount of free cholesterol⁴⁶. Blood samples must, therefore, be collected under conditions in which the ratio of free cholesterol to its esters is fairly constant. By avoiding the effects of food and severe exercise, this source of error is largely eliminated. However, as will presently be shown, aside from the above mentioned variables, there are other sources of difficulty in the interpretation of plasma cholesterol. A summary of all of our data is shown in table 3.

TABLE III
Average Annual Plasma Cholesterol *

| Year | Joslin Clinic | Montreal Gen Hosp Data | |
|------|--|------------------------|--------------------------------------|
| | Average † Cholesterol (Per Cent) | Number | Average Cholesterol (Per Cent) |
| 1926 | 0.270 | 297 | 0.270 |
| 1927 | 0.257 | 570 | 0.247 |
| 1928 | 0.240 | 498 | 0.275 |
| 1929 | 0.220 | 441 | 0.258 |
| 1930 | 0.215 | 1092 | 0.214 |
| 1931 | 0.210 | 936 | 0.228 |
| 1932 | 0.212 | 722 | 0.228 |
| 1933 | | 595 | 0.207 |

* Includes admission, discharge and progress data

† Data from Joslin Clinic Chart 10 Metropolitan Life Ins Co, 1933 Report The Control of Diabetes (3000 analyses in 1100 cases)

It will be observed that the cholesterol values are grouped according to the year in which they were obtained. The purpose of this grouping is to show the trend of blood cholesterol, namely, the decrease within recent years, the averages found between 1930 and 1933 were lower than those noted between the years 1926 and 1929. These findings agree, in general, with Joslin's experiences. The latter are reproduced in the same table and were taken from a report (chart 1) published by the Metropolitan Life Insurance Company to portray the success obtained in the control of diabetes.⁴⁷ "The fall of the blood cholesterol to normal," this report states, "is further evidence of the recent improvement in diabetic treatment."

The purpose of recording the above summaries of Joslin's and our own data is to demonstrate a number of difficulties in the interpretation of blood cholesterol observations which had to be considered in this study of arterio-

sclerosis As I shall presently show, neither Joslin's data nor our own, as shown in this table and chart 1, necessarily indicate improvement in methods of treatment Both Joslin's data * and our own, for example, include *all* cholesterol determinations, that is, those made *before* and after treatment

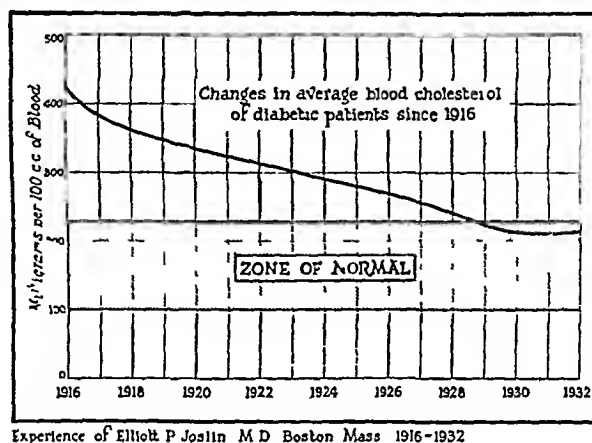


CHART 1

One source of error is, therefore, immediately obvious, a normal cholesterol found *before* treatment must obviously not be attributed to improvement of method of treatment

In table 4 are recorded all of our data which were obtained when the

TABLE IV
Annual Average Plasma Cholesterol *

| Year | No | Average Cholesterol (Per Cent) |
|------|-----|--------------------------------|
| 1926 | 62 | 0 348 |
| 1927 | 43 | 0 354 |
| 1928 | 59 | 0 325 |
| 1929 | 101 | 0 301 |
| 1930 | 207 | 0 282 |
| 1931 | 284 | 0 288 |
| 1932 | 216 | 0 263 |
| 1933 | 187 | 0 242 |

* Includes data obtained on admission only

patients were first admitted to our clinic, that is, before any form of treatment was given in the majority of cases and in every case before having been subjected to our methods of treatment Here, it will be noted, that, for the corresponding years, the average values are higher than in table 3, but, again, the values between 1926 and 1929 are *higher* than between 1930 and 1933 Since the great majority of these patients received no intensive treatment prior to their admission to the clinic, it is obvious that the de-

* Personal communication

crease of cholesterol must have been due to some condition, or conditions, other than treatment. One of these conditions is early diagnosis. This is shown in table 5, in which are recorded plasma cholesterol determinations

TABLE V
Influence of Early Diagnosis upon Plasma Cholesterol

| Type of Case | No | M | σ | PEM | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
|-----------------------|-----|-----|----------|------|----------|-------------|---------------------------|
| Ward diabetics (1933) | 187 | 242 | 86 | 4.23 | 30 | 5.73 | 5.2 |
| Life assurance cases | 163 | 212 | 73 | 3.84 | 46 | 5.40 | 8.5 |
| Potential diabetics | 128 | 166 | 65 | 3.80 | | | |

M = Mean (average cholesterol—mg per 100 c c plasma)

σ = Standard deviation

PEM = Probable error of mean

Δ = Difference between means

PE Δ = Probable error of difference

in 478 individuals who *at no time received any treatment* before their admission to the Clinic. The cases are divided into three groups as follows.

Group 1 consists of cases of *fully established diabetes*, that is, the diabetes was sufficiently advanced to have warranted admission of the patients to the hospital wards for intensive treatment.

Group 2 consists of cases of diabetes in its very *early stages*, that is, individuals with no signs or symptoms of the disease, in whom the glycosurias were discovered accidentally when these people applied for life assurance policies.

Group 3 consists of individuals who may be regarded as *potential diabetics only*. *Glycosuria was never found in any of these individuals*. The disturbances of carbohydrate tolerance, in this group, were suspected because of a variety of clinical conditions, eczema, neuritis, etc. On careful investigation, many of these individuals were found to have had very mild hyperglycemia only in the fasting state. In the remainder of the group, the blood sugars were normal in the fasting state, but the disturbances of carbohydrate tolerance were discovered by obtaining blood sugar time curves following ingestion of glucose.

The above grouping clearly shows the importance of early diagnosis in the interpretation of cholesterol data, as the diabetes became more fully established, and, as no treatment was given, the cholesterol content of the plasma increased. It should be observed that the differences noted between the average cholesterol values of the different groups are statistically significant. This is shown in each case, by the ratio of difference to its probable error.*

* In this, and the following studies, a ratio of difference to its probable error less than 3.0 was not regarded as significant. With a ratio of 3.0, it can be shown that the odds against the occurrence of a difference of such magnitude being due to chance alone are about 20 to 1.

It will be noted that the average cholesterol in the group of potential diabetics (0 166 per cent) was lower than that of normal individuals (0 180 per cent) The probable explanation is that, in a number of these cases, there were conditions which tend to lower blood cholesterol None of these individuals, it should be observed, was perfectly normal This would probably also apply to the group of ward diabetics, though not to the life assurance applicants, the majority of whom may be assumed to have been healthy These data, may, therefore, not be strictly comparable, but they appear to be sufficiently so to show the force of early diagnosis

Table 6 shows another variable which must be considered in the inter-

TABLE VI
Immediate Effects of Treatment upon High Concentrations of Plasma Cholesterol

| Subject | Plasma Cholesterol (Per Cent) | | |
|---------|-------------------------------|-----------|----------|
| | Admission | Discharge | Decrease |
| 5728/28 | 1 380 | 0 504 | 0 876 |
| 6535/28 | 1 190 | 0 520 | 0 670 |
| 2126/29 | 0 926 | 0 438 | 0 488 |
| 3345/29 | 1 510 | 0 640 | 0 870 |

pretation of plasma cholesterol, namely, the *immediate* effects of treatment upon *very high* concentrations of plasma cholesterol The marked and rapid decreases of cholesterol clearly demonstrate the error of drawing conclusions from averages based upon a small number of observations High cholesterol values, as shown in this table, may be met with in very acute forms of diabetes and in cases of acidosis All of the cases shown in this table were cases of diabetes with ketosis and acidosis

A variety of other conditions may influence plasma cholesterol, such conditions as alcoholism, nephrosis, gout pregnancy, biliary obstruction and myxedema are associated with an increase, whereas, febrile disorders, hepatitis, severe anemias, cachexias in general, syphilis, tuberculosis and hyperthyroidism tend to lead to a decrease In the female, consideration must also be given to the general increase before, and fall during, menstruation⁴⁸ Tables 7 and 8 show the influence of a very common condition in diabetes, namely, infection Not every infection leads to a reduction of plasma cholesterol, but, in general, the plasma cholesterol is lower in infection than without infection In table 7 are shown the average cholesterol values of 100 cases of diabetes with infection collected at *random* from our records by Dr E H Bensley They represent admission * values only Admis-

* In all discussions hereafter, the term *admission* will apply to cholesterol data obtained when the patients were admitted to the clinic Cholesterols obtained when the patients were discharged from the hospital will be referred to as *discharge* cholesterols The term *discharge* cholesterol will also apply to data obtained from patients who were not admitted to the wards, but were treated in the out-patient clinic of the hospital As a rule, such cholesterol determinations were made 14 days after institution of treatment All data obtained subsequent to discharge from the wards, or after 14 days of out-patient treatment, will be referred to as *progress* cholesterols

sion values of cases with infection are then compared with the averages of all admission data for the corresponding years. It will be observed that with one exception (that is, 1929) the average admission cholesterols of the patients with infection were lower than the admission averages of all patients during the corresponding years.

The cases of infection shown in table 7 include individuals who had

TABLE VII
Influence of Infection upon Plasma Cholesterol *

| Year | All Data | | Acute Infection | |
|------|----------|--------------------------------|-----------------|--------------------------------|
| | No | Average Cholesterol (Per Cent) | No | Average Cholesterol (Per Cent) |
| 1929 | 101 | 0 301 | 7 | 0 304 |
| 1930 | 207 | 0 282 | 31 | 0 184 |
| 1931 | 284 | 0 288 | 29 | 0 221 |
| 1932 | 216 | 0 263 | 33 | 0 167 |

* All data obtained on admission of patients to hospital

received treatment previously and were admitted largely because of the infections. Previous treatment is obviously an influencing factor. These previously-treated cases are, therefore, excluded in table 8. Excluding the effects of previous treatment, it will be observed infection is still an impor-

TABLE VIII
Influence of Infection upon Plasma Cholesterol

| Year | All Data | | Acute Infection * | |
|------|----------|--------------------------|-------------------|--------------------------|
| | No | Cholesterol † (Per Cent) | No | Cholesterol † (Per Cent) |
| 1929 | 101 | 0 301 | 5 | 0 319 |
| 1930 | 207 | 0 282 | 13 | 0 195 |
| 1931 | 284 | 0 288 | 19 | 0 196 |
| 1932 | 216 | 0 263 | 17 | 0 172 |

* Includes cases not treated previously

† Data obtained on admission only

tant factor influencing the interpretation of blood cholesterol. From these data, it is obvious that normal or low values found in such cases must not be attributed to improvement of treatment, the infection, per se, may have lowered the cholesterol.

While this paper was in preparation, there were two patients in the wards who strikingly showed the influence of two of the previously mentioned conditions, namely, hyperthyroidism (6377/34) and myxedema * (6275/34). In both cases, it was very difficult, for a time, to control the

* There are now three cases of this rare combination of conditions in this clinic

diabetes In spite of poor control, however, the plasma cholesterol was low in the case of *hyperthyroidism*, but following control of the hyperthyroidism (iodine and thyroidectomy, etc.) the cholesterol increased, reaching as high a level as 0.315 per cent, the diabetes was still very difficult to control. In the case of *hypothyroidism*, the cholesterol was as high as 0.396 per cent. This might have been due to the diabetes or the thyroid disease. Following thyroid extract medication, however, it *decreased*. Since treatment of the diabetes alone with diet and insulin had no effect, it appears reasonable to conclude that the excess cholesterol was due largely to the thyroid disease.

TABLE IX

Effects of Hyperthyroidism and Hypothyroidism upon Plasma Cholesterol in Diabetes Mellitus

| Hosp No 6377/34 Diagnosis Hyperthyroidism | | | Hosp No 6275/34 Diagnosis Myxedema | | |
|--|-------------------------------|-------------------|---------------------------------------|-------------------------------|------------------------------|
| Date | Plasma Cholesterol (Per Cent) | Treatment | Date | Plasma Cholesterol (Per Cent) | Treatment |
| Nov 6, 1934 | 0.163 | Thyroid Lobectomy | Oct 30, 1934 | 0.333 | Thyroid extract grs v, b i d |
| 10 | 0.177 | | Nov 3 | 0.282 | |
| 12 | 0.181 | | 9 | 0.264 | |
| 13 | 0.164 | | 13 | 0.238 | |
| 20 | 0.181 | | 14 | 0.228 | |
| Dec 7 | 0.185 | | 16 | 0.273 | |
| 14 | 0.244 | | 19 | 0.208 | |
| 20 | 0.277 | | 23 | 0.238 | |
| 22 | 0.179 | | 26 | 0.396 | |
| 28 | 0.228 | | Dec 3 | 0.292 | |
| 31 | 0.308 | | 5 | 0.297 | |
| Jan 2, 1935 | 0.315 | | 7 | 0.264 | |
| 4 | 0.333 | | 10 | 0.302 | |
| 5 | 0.396 | | 12 | 0.282 | |
| 7 | 0.362 | | 14 | 0.333 | |
| | | | 19 | 0.222 | |
| | | | 21 | 0.252 | |
| | | | 24 | 0.235 | |
| | | | 26 | 0.228 | |
| | | | 28 | 0.185 | |
| | | | 31 | 0.177 | |
| | | | Jan 2, 1935 | 0.219 | Thyroid extract grs v, t i d |
| | | | 5 | 0.219 | |
| | | | 7 | 0.214 | |

A summary of the findings in these two cases is given in table 9. The data clearly demonstrate the possible influence of the metabolic effects of one condition upon another and the difficulties of interpretation of blood cholesterol. An analogy is found in a combination of typhoid fever and diabetic coma. In one of our cases (3620/32) when the patient was admitted to the hospital and, while in coma, there was the usual leukocytosis of diabetic coma, the white cell count was 32,700. Four days later, following com-

plete recovery from the coma there was the leukopenia typical of typhoid fever, the cell count was 5,000

In table 10 is shown the relationship found between plasma cholesterol and arteriosclerosis in 300 cases of diabetes selected at random. In this group, there were 166 cases of cardiovascular disease*. The average

TABLE X

Relationship between Plasma Cholesterol and Arteriosclerosis in 300 Diabetics Selected at Random

| Group | Arterio sclerosis | No | M | σ | PEm | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
|------------------------|----------------------|-----|-----|----------|------|----------|-------------|---------------------------|
| Whole | Present | 166 | 217 | 91 | 4.72 | 8 | 6.15 | 1.3 |
| | Absent | 134 | 209 | 68 | 3.92 | | | |
| Age 50 years and under | Present | 57 | 213 | | | 16 | 9.35 | 1.7 |
| | Absent | 84 | 213 | | | | | |
| Over age 50 years | Present | 109 | 219 | 72 | 4.68 | | | |
| | Absent | 50 | 203 | 86 | 8.11 | | | |

M = Mean (average cholesterol—mg per 100 c c plasma)

σ = Standard deviation

PEm = Probable error of mean

Δ = Difference between means

PE Δ = Probable error of difference

plasma cholesterol of the whole group was 0.213 per cent and it will be observed that, when the cases were grouped according to the presence or absence of vascular disease, a small difference only was found between the average cholesterol of the two groups, namely, 8 milligrams. That this difference was of little or no significance is shown by ratio of the difference to its probable error ($\Delta/PE\Delta = 1.3$).

Since a high incidence of cardiovascular disease is expected in elderly people even in nondiabetics, and since hypercholesterolemia has not been found in nondiabetic arteriosclerotics with the same frequency as in the diabetic with arteriosclerosis, it was considered important to exclude the effects of advanced age. The above mentioned 300 cases were, therefore, divided into two groups according to age, namely, (a) individuals of age 50 years and under and (b) those over age 50 years. The results of this grouping are shown in the same table. It will be noted that method of grouping did not affect the results, regardless of age, the average cholesterol of those with, and of those without, cardiovascular disease were approximately the same. In the younger age group, the average cholesterol of those with cardiovascular disease was identical with that of those with

* It is of interest to note that this incidence of cardiovascular disease, namely, 55.3 per cent, agrees very closely with that of a previously reported random selection. In the latter, the incidence was 62.6 per cent.²

no cardiovascular disease, and, according to the ratio of the difference to its probable error, the difference of cholesterol found in the older age group was not significant ($\Delta/PE\Delta = 1.7$)

The above findings fit in with the previously mentioned experiences of Hazel Hunt in Joslin's clinic²⁴. Blood cholesterol values were not found high in arteriosclerosis. Nor was there any correlation between the degree of arteriosclerosis and hypercholesterolemia, the group which showed the lowest average blood cholesterol was the group which had the greatest degree of arteriosclerosis.

As stated, the selection of the above mentioned 300 cases was *random*. No attention was paid to the presence or absence of associated conditions which might have increased or decreased the blood cholesterol in these cases. Therefore, in view of previous observations, the possibility had to be considered that some of these diabetics may have had sufficient hypercholesterolemia for some time to have led to arteriosclerosis, but that, at the time these analyses were made, they may have suffered from infection or some other conditions which may have led to reduction of cholesterol. These 300 cases were, therefore, re-investigated and a variety of disturbing factors were found. There were, for example, 10 cases of hyperthyroidism. The average age of these 10 diabetics was 50.9 years and the average duration of the diabetes was 6.3 years. The average plasma cholesterol was practically normal, namely, 0.192 per cent. It was greater than 0.2 per cent in three cases only. Yet of these 10 individuals, two had retinal changes characteristic of arteriosclerosis and three had "senile" cataracts.

In view of the above findings, an attempt was made to collect a group of diabetics who either had no other disease or in whom there were no detectable associated conditions or complications other than cardiovascular disease. The selection was otherwise *random*. Among 1000 case records so examined, there were 167 only of such individuals and, among them, 62 were found with cardiovascular disease. A summary of the cholesterol findings in these 167 cases is shown in table 11.

Again, it will be observed that by simply dividing the cases according to the presence or absence of cardiovascular disease, there was no appreciable difference between the average cholesterol of the cases with, and of those without, vascular disease ($\Delta/PE\Delta = 0.69$). However, when the cases were grouped according to age, a definite difference was found, in the group of individuals of age 50 years and under, the average cholesterol of those with cardiovascular disease was 43 milligrams higher than in those without cardiovascular disease. Expressed as percentage difference, the average plasma cholesterol in the cases with cardiovascular disease was about 19 per cent higher than in the cases without cardiovascular disease. That the difference of 43 milligrams was significant is shown by the ratio of the difference to its probable error ($\Delta/PE\Delta = 3.5$). The finding in the older age group appears to be disturbing, the average cholesterol of those with no cardiovascular disease was 17 milligrams higher than the average of

TABLE XI

Relationship between Plasma Cholesterol and Arteriosclerosis in 167 Diabetics Selected at Random but with no Detectable Associated Conditions or Complications other than Cardiovascular Disease

| Group | Arterio sclerosis | No | M | σ | PEm | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
|------------------------|----------------------|-----|-----|----------|-------|----------|-------------|---------------------------|
| Whole | Present | 62 | 227 | 89 | 7.55 | 6 | 9.17 | 0.69 |
| | Absent | 105 | 221 | 78 | 5.22 | | | |
| Age 50 years and under | Present | 26 | 267 | 81 | 10.65 | 43 | 12.1 | 3.5 |
| | Absent | 68 | 224 | 73 | 5.89 | | | |
| Over age 50 years | Present | 36 | 198 | 93 | 10.35 | 17 | 14.3 | 1.2 |
| | Absent | 37 | 215 | 87 | 9.67 | | | |

M = Mean (average cholesterol—mg per 100 c c plasma)

σ = Standard deviation

PEm = Probable error of mean

Δ = Difference between means

PE Δ = Probable error of difference

those with the disease. However, according to the ratio of the difference to its probable error, this finding is of little or no significance ($\Delta/PE\Delta = 1.2$). *Hence, therefore, we find the first suggestion, statistically, of a causal relationship between hypercholesterolemia and cardiovascular disease.*

In the above study, no attention was paid to the presence or absence of hypertension. As stated previously, Mjassnikow²⁰ found an increase of blood cholesterol regularly in advanced arteriosclerosis. No such increase was, however, found in "essential" or nephritic hypertension. Since the atherosclerosis of diabetes is not generally associated with hypertension and since hypertension may, per se, lead to arteriosclerosis, it was considered important to group the 62 cases of cardiovascular disease according to the presence or absence of increase of blood pressure. A summary of the results is shown in table 12.

It will be observed that it was important to exclude hypertension, in order to determine the relationship between cardiovascular disease and blood cholesterol. By grouping these cases without regard to age, the average cholesterol of those with no hypertension was 35 milligrams higher than those with hypertension. Expressed as percentage difference, the average cholesterol of the cases with no hypertension was about 17 per cent higher than those with hypertension. That this difference of 35 milligrams was *probably* significant is suggested from the ratio of the difference to its probable error ($\Delta/PE\Delta = 2.3$).

The importance of excluding hypertension is more clearly shown in the same table where the cases are grouped with respect to age. It will be observed that, in the cases of hypertension, the average cholesterol of those

TABLE XII

Relationship between Plasma Cholesterol and Hypertension in the 62 Cases of Cardiovascular Disease Shown in Table 11

| Group | No | M | σ | PEm | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
|--|----|-----|----------|------|----------|-------------|---------------------------|
| Whole | 62 | 227 | | | | | |
| Hypertension | 18 | 202 | 78 | 12.3 | 35 | 15.2 | 2.3 |
| No hypertension | 44 | 237 | 89 | 9.0 | | | |
| Hypertension—Age 50 years and under | 4 | 211 | 74 | 24.8 | 11 | 28.7 | 0.38 |
| Over age 50 years | 14 | 200 | 81 | 14.6 | | | |
| No Hypertension—Age 50 years and under | 22 | 270 | 94 | 13.4 | 66 | 17.4 | 3.8 |
| Over age 50 years | 22 | 204 | 78 | 11.1 | | | |

M = Mean (average cholesterol—mg per 100 c c plasma)

σ = Standard deviation

PEm = Probable error of mean

Δ = Difference between means

PE Δ = Probable error of difference

of age 50 years and under was only 11 milligrams higher than that of the older age group and, according to the ratio of the difference to its probable error, this difference of 11 milligrams was not significant ($\Delta/PE\Delta = 0.38$). On the other hand, in the cases with no hypertension, there was a definite difference between the cholesterol values of the two age groups, the average cholesterol of the younger age group was 66 milligrams higher than that of the older age group and, according to the ratio of this difference to its probable error, the difference of 66 milligrams was significant ($\Delta/PE\Delta = 3.8$).

The intimate relationship between cardiovascular disease and blood cholesterol is more clearly shown in table 13. It will be observed that, when grouped without regard to age, the average cholesterol of those with cardiovascular disease was not appreciably greater than that of those with the disease, the difference was 16 milligrams only, and, according to the ratio of the difference to its probable error, this finding was not significant ($\Delta/PE\Delta = 1.5$). However, when the cases were grouped according to age, a definite relationship was found between cardiovascular disease and cholesterol in the younger age group of diabetics, the average cholesterol of those with cardiovascular disease was 46 milligrams higher than that of the group with no detectable vascular disease. Expressed as percentage difference, the average cholesterol in the cases with cardiovascular disease was about 20 per cent higher than in those in whom no vascular changes were found. That this difference of 46 milligrams was significant is shown by the ratio of the difference to its probable error ($\Delta/PE\Delta = 3.1$). In the older age group, it appeared that those with cardiovascular disease had

TABLE XIII

Relationship between Plasma Cholesterol and Cardiovascular Disease without Hypertension According to Age

| Group | Arterio-sclerosis | No | M | σ | PEm | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
|------------------------|-------------------|-----|-----|----------|------|----------|-------------|---------------------------|
| Whole | Present | 44 | 237 | 89 | 9 00 | 16 | 10 3 | 1 5 |
| | Absent | 105 | 221 | 78 | 5 12 | | | |
| Age 50 years and under | Present | 22 | 270 | 94 | 13 4 | 46 | 14 7 | 3 1 |
| | Absent | 68 | 224 | 73 | 5 96 | | | |
| Over age 50 years | Present | 22 | 204 | 78 | 11 1 | 11 | 14 8 | 0 74 |
| | Absent | 37 | 215 | 87 | 9 67 | | | |

M = Mean (average cholesterol—mg per 100 c c plasma)

σ = Standard deviation

PEm = Probable error of mean

Δ = Difference between means

PE Δ = Probable error of difference

slightly lower cholesterol values than those without detectable changes, the average cholesterol of those without cardiovascular disease was about 64 per cent higher than those with the disease. Judging, however, by the ratio of the difference to its probable error, this finding was not significant ($\Delta/PE\Delta = 0.74$). Combining all of the above mentioned findings, therefore, and by weighting percentages, it appears reasonable to conclude that *there is an intimate association between cardiovascular disease and hypercholesterolemia*.

Parenthetically, the above data present another problem for solution in diabetes. The purpose of not including elderly diabetics and those with hypertension in this investigation was to exclude arteriosclerosis which is known to develop in the nondiabetic apparently irrespective of the cholesterol content of the blood. Since all of these patients were practically on the same type of diet, it was expected that the incidence of hypercholesterolemia among the elderly diabetics and those with hypertension would not be less than among the younger age group of patients. An artificial correlation between hypercholesterolemia and cardiovascular disease might, therefore, be found. The purpose of this study was to determine whether young diabetics with cardiovascular disease have more cholesterol in the blood than those without cardiovascular disease. The above data, therefore, support the view, statistically at least, that the metabolism of the young diabetic differs from that of elderly individuals with respect to lipoids. The data clearly show that excess accumulation of blood cholesterol is more marked in the young, than in the elderly, diabetic. The data, it should be observed, fit in with the previously mentioned observations of Klotz and Manning⁸ namely, the association of fatty deposition in the intima with definite age

periods—its frequency between the ages of 20 to 30 years and its unusual occurrence after age 50 years. An analogy is suggested in the selective retention of vegetable pigments, why some diabetics are more prone than others to xanthosis (carotinemia) is, as yet, not known.

EFFECT OF HIGH CARBOHYDRATE-LOW CALORIE DIET

The conclusion that there is a causal relationship between the level of circulating cholesterol and arteriosclerosis is statistical, and is supported by a large number of observations. Other experiences, however, also lend themselves to similar treatment. The following were data obtained with the high carbohydrate-low calorie diet.

A variety of metabolic effects of the high carbohydrate-low calorie diet in diabetes used in this clinic were discussed elsewhere^{49, 50, 51} and will, therefore, not be dealt with here. At present, we are concerned with one observation only, namely, the effects of this diet upon blood cholesterol. As I pointed out previously, one of the most striking effects is the immediate and sustained decrease of plasma cholesterol. Of the first 500 cholesterol determinations, 393 (78.6 per cent) were under 0.2 per cent and 199 (39.8 per cent) were no greater than 0.15 per cent. The low values were sufficiently striking to prompt Dr. Joslin* to ask "What would happen if the cholesterol dropped below the normal? Is there any danger?" A more detailed analysis of the cholesterol data with this diet is shown in the following tables.

TABLE XIV
Immediate Effect of Treatment upon Plasma Cholesterol

| Year | Admission Data | | Discharge Data * | |
|------|----------------|--------------------------------|------------------|--------------------------------|
| | No | Average Cholesterol (Per Cent) | No | Average Cholesterol (Per Cent) |
| 1926 | 62 | 0.348 | 41 | 0.284 |
| 1927 | 43 | 0.354 | 26 | 0.262 |
| 1928 | 59 | 0.325 | 48 | 0.276 |
| 1929 | 101 | 0.301 | 82 | 0.241 |
| 1930 | 207 | 0.282 | 135 | 0.253 |
| 1931 | 284 | 0.288 | 146 | 0.212 |
| 1932 | 216 | 0.263 | 127 | 0.205 |
| 1933 | 187 | 0.242 | 111 | 0.182 |

* Includes cases only in which cholesterol data were obtained before treatment commenced. Includes non-ward cases, two weeks after commencement of treatment. (Average duration of hospital treatment 14 days.)

In table 14 are shown the *immediate* effects of treatment with the high carbohydrate-low calorie diet compared with those of the older and relatively low carbohydrate-high fat diets. In this table are recorded annual average blood cholesterol levels when the patients were first admitted to the clinic and

* Personal communication.

again, about two weeks later. It will be observed that in 1931 and 1932, that is, when practically every new patient with advanced diabetes was given the high carbohydrate-low calorie diet, the average *discharge* cholesterol was nearly normal. In 1933, the average *discharge* cholesterol was normal. These data alone, however, do not show the effects of this diet very clearly. According to weighted averages, the average reduction of plasma cholesterol during the period 1931-1933 was not very much greater than those found during the period of high fat feeding 1926-1930, with the latter diets, the average reduction for the period 1926-1930 was about 48 milligrams, whereas, with the new diet it was about 65 milligrams. It should, however, be observed that in this comparison of *admission* with *discharge* data, conditions which may influence plasma cholesterol levels other than diet were not excluded. Also, as was previously shown (table 6) the initial level of plasma cholesterol may alone influence the *rate* at which the cholesterol returns to the normal level and it will be observed that the *admission* values prior to 1931 were higher than in the following years.

TABLE XV

Immediate Effects of Treatment with Different Diets upon Plasma Cholesterol

| High Carbohydrate Low Calorie Diet | | | | Low Carbohydrate-High Fat Diet | | | |
|------------------------------------|------------------------|-----------|------------|--------------------------------|------------------------|-----------|------------|
| Hosp No | Cholesterol (Per Cent) | | | Hosp No | Cholesterol (Per Cent) | | |
| | Admission | Discharge | Difference | | Admission | Discharge | Difference |
| 2404-32 | 0.347 | 0.113 | -0.234 | 46-29 | 0.326 | 0.463 | +0.137 |
| 3257 | 0.333 | 0.196 | -0.137 | 254 | 0.302 | 0.326 | +0.024 |
| 3553 | 0.362 | 0.208 | -0.154 | 431 | 0.340 | 0.427 | +0.087 |
| 5779 | 0.302 | 0.302 | — | 1388 | 0.396 | 0.302 | -0.094 |
| 6864 | 0.308 | 0.260 | -0.048 | 3761 | 0.370 | 0.406 | +0.036 |
| 7125 | 0.362 | 0.175 | -0.187 | 5617 | 0.321 | 0.225 | -0.096 |
| 7193 | 0.333 | 0.214 | -0.119 | 3805-28 | 0.387 | 0.314 | -0.073 |
| 1103-33 | 0.333 | 0.185 | -0.148 | 6017 | 0.333 | 0.225 | -0.108 |
| 1630 | 0.333 | 0.171 | -0.162 | 6771 | 0.302 | 0.268 | -0.034 |
| 1835 | 0.326 | 0.260 | -0.066 | 6870 | 0.300 | 0.260 | -0.040 |
| 4991 | 0.378 | 0.192 | -0.186 | 7218 | 0.333 | 0.277 | -0.056 |
| 5326 | 0.302 | 0.216 | -0.086 | 7092 | 0.300 | 0.347 | +0.047 |
| Average | 0.335 | 0.207 | 0.128 | Average | 0.334 | 0.320 | 0.014 |

In table 15, are shown 24 cases carefully selected with respect to the level of the blood cholesterol prior to treatment. The data of the two types of diets are also otherwise reasonably comparable. It will be observed that, with the new diet, the average *immediate* reduction of cholesterol was 128 milligrams per 100 c c plasma and that the diet failed to lower the plasma cholesterol in one case (5779/32) only, whereas, with the older diets, the average reduction was only 14 milligrams. Of these 12 cases, there was no reduction in five instances, the cholesterol was not only reduced, but slightly

TABLE XVI
Influence of Treatment upon Plasma Cholesterol
(Progress data only, data obtained before and immediately after (14 days) treatment not included)

| | A | | B | | C | | D | | E | | High Carbohydrate | | Restricted Carbohydrate | | All Data | |
|------|-----|--------|-----|--------|-----|--------|-----|--------|-----|--------|-------------------|--------|-------------------------|--------|----------|--------|
| | No | Chol % | No | Chol % | No | Chol % | No | Chol % | No | Chol % | No | Chol % | No | Chol % | No | Chol % |
| 1926 | 82 | 0.251 | 64 | 0.241 | 18 | 0.226 | 10 | 0.230 | 4 | 0.282 | | | 16 | 0.217 | 194 | 0.242 |
| 1927 | 221 | 0.245 | 102 | 0.228 | 31 | 0.248 | 86 | 0.216 | 37 | 0.264 | | | 24 | 0.232 | 501 | 0.237 |
| 1928 | 222 | 0.308 | 48 | 0.230 | 12 | 0.232 | 42 | 0.182 | 24 | 0.246 | | | 43 | 0.205 | 391 | 0.267 |
| 1929 | 67 | 0.303 | 31 | 0.226 | 42 | 0.200 | 75 | 0.230 | 16 | 0.232 | | | 27 | 0.228 | 258 | 0.243 |
| 1930 | 17 | 0.249 | 12 | 0.232 | 28 | 0.241 | 64 | 0.218 | 5 | 0.254 | 586 | 0.178 | 38 | 0.208 | 750 | 0.188 |
| 1931 | 13 | 0.258 | 3 | 0.272 | 6 | 0.229 | 30 | 0.232 | 14 | 0.243 | 422 | 0.194 | 18 | 0.202 | 506 | 0.201 |
| 1932 | 12 | 0.272 | 4 | 0.315 | 9 | 0.242 | 6 | 0.228 | 3 | 0.261 | 313 | 0.172 | 32 | 0.209 | 379 | 0.183 |
| 1933 | 6 | 0.268 | 2 | 0.364 | 4 | 0.231 | 23 | 0.202 | 1 | 0.282 | 235 | 0.186 | 26 | 0.218 | 297 | 0.192 |
| | 640 | 0.275 | 266 | 0.234 | 150 | 0.228 | 336 | 0.216 | 104 | 0.252 | 1556 | 0.181 | 224 | 0.214 | 3276 | |

higher than on admission. We have never been able to explain the temporary increase of cholesterol in some cases shortly after commencement of treatment. Such increases are occasionally seen with the new diet also.

The *progress* data, that is, the data obtained after the patients had been on the diet for many weeks, months and years, demonstrated more clearly the effects of the high carbohydrate-low calorie diet on blood cholesterol. A summary of our experiences is shown in table 16. Averages of plasma cholesterol with the new diet are compared with those found with the old A, B, C, D and E diets, the corresponding carbohydrate values of which were 50, 75, 100, 125 and 150 grams respectively. In these old diets, the fat content ranged between 140 and 150 grams. It will be observed that, with all of the high fat diets, the average cholesterol values were high, regardless of their carbohydrate contents, the average of 104 determinations with Diet E (0.252 per cent) the carbohydrate content of which was 150 grams, was not very much lower than the average of 640 determinations with Diet A (0.275 per cent) the carbohydrate content of which was 50 grams only. The findings with these old diets contrast markedly with the cholesterol values obtained with the high carbohydrate-low calorie diet. It will be observed that the average of 1556 determinations of *progress* cholesterol with this diet was only 0.181 per cent. Attention is, again, drawn to the fact that these are *progress* data, that is, cholesterol determinations made after the patients were on the high carbohydrate-low calorie diet for many weeks, months, and years. They clearly indicate the *sustained* decrease of plasma cholesterol with the new diet.

Parenthetically, the *progress* data obtained with the "restricted carbohydrate diet," also shown in the above table, are of interest. In the past, this diet was generally given to individuals with no clinical signs or symptoms of diabetes other than the glycosuria, in whom the glycosuria was discovered accidentally and whose blood sugars were normal in the fasting state. This "restricted carbohydrate diet" included avoiding sugar in tea and coffee, pastries, puddings, cake and candy of all kinds, restriction of bread intake to about one slice (one ounce) at each meal and regulation of the total intake of food so as to keep the body weight slightly below the normal for the height and age. It will be observed that the *progress* cholesterols are not as satisfactory as with the high carbohydrate-low calorie diet, of 224 determinations, the average cholesterol was 0.214 per cent. In view of these experiences, treatment of such individuals obviously requires modification, the diets of these individuals were apparently still too high with respect to fat. The case shown in table 17 is cited as a typical example of the course of events when the high carbohydrate-low calorie diet was substituted for the older forms of treatment. The data include 46 cholesterol determinations during a period of about six years. They clearly show the *sustained* decrease of plasma cholesterol with the high carbohydrate-low calorie diet.

TABLE XVII

Effects of Substitution of High Carbohydrate Low Calorie Diet for Liberal Carbohydrate-High Fat Diet upon Plasma Cholesterol
(Hosp No 5053/28)

| Date | Plasma Cholesterol (%) | Diet | | | Insulin | Date | Plasma Cholesterol (%) | Diet | | | Insulin |
|-------------|------------------------|------|-----|----|----------|--------------|------------------------|------|----|----|---------|
| | | C | F | P | | | | C | F | P | |
| Aug 25 1928 | 0 236 | 150 | 150 | 60 | 20/ 0/20 | April 2 1931 | 0 241 | 254 | 56 | 72 | 20/0/20 |
| Oct 26 | 0 241 | | | | | May 14 | 0 166 | | | | |
| Nov 16 | 0 260 | | | | | July 7 | 0 184 | | | | |
| Dec 15 | 0 282 | | | | | Aug 6 | 0 125 | | | | |
| Jan 11 1929 | 0 340 | | | | | Sept 15 | 0 122 | | | | |
| Febr 8 | 0 315 | | | | | Oct 24 | 0 166 | | | | |
| March 8 | 0 273 | | | | | Nov 17 | 0 166 | | | | |
| April 5 | 0 396 | | | | 20/10/20 | Jan 13 1932 | 0 156 | | | | |
| May 29 | 0 232 | | | | | Febr 23 | 0 169 | | | | |
| June 27 | 0 285 | | | | | April 25 | 0 228 | | | | |
| July 30 | 0 254 | | | | | June 22 | 0 287 | | | | |
| Aug 27 | 0 242 | | | | | Aug 27 | 0 111 | | | | |
| Oct 28 | 0 216 | | | | | Dec 2 | 0 196 | | | | |
| Dec 26 | 0 321 | | | | | March 6 1934 | 0 185 | | | | |
| Jan 16 1930 | 0 277 | | | | | April 28 | 0 238 | | | | |
| March 7 | 0 252 | 218 | 56 | 69 | | July 24 | 0 208 | | | | |
| June 11 | 0 120 | 236 | | 72 | | Oct 24 | 0 163 | | | | |
| July 2 | 0 145 | 254 | | | 20/ 0/20 | Nov 7 | 0 238 | | | | |
| Sept 4 | 0 139 | | | | | Jan 3 1934 | 0 238 | | | | |
| Oct 2 | 0 111 | | | | | Febr 1 | 0 181 | | | | |
| Nov 7 | 0 111 | | | | | March 15 | 0 214 | | | | |
| Dec 30 | 0 160 | | | | | July 24 | 0 200 | | | | |
| Febr 5 1931 | 0 117 | | | | | Dec 19 | 0 204 | | | | |

DOES THE HIGH CARBOHYDRATE-LOW CALORIE DIET PREVENT, OR DELAY THE DEVELOPMENT OF, ARTERIOSCLEROSIS?

The proof that there is an intimate association between hypercholesterolemia and arteriosclerosis appears to be definite. It, therefore, appears reasonable that if the relationship between the two conditions is causal, the high carbohydrate-low calorie diet (or any other condition which can keep the cholesterol content of the blood at the proper level) should prevent, or at least delay development of, arteriosclerosis. An attempt was, therefore, made to determine whether the incidence of cardiovascular disease among diabetics treated with the high carbohydrate-low calorie diet was lower than among diabetics treated otherwise.

It is of interest here to note that other conditions commonly associated with hypercholesterolemia and with cardiovascular disease have largely disappeared in our clinic with the institution of this diet. Xanthosis (carotinemia) is now rare. We have had three cases only during the last five years. The significance of carotinemia and its relationship to arteriosclerosis were discussed elsewhere^{37,38}. Gangrene is also disappearing. Since 1931, we have had 36 cases, but, in 25, the gangrene was present when the patients were first admitted to the Clinic. Therefore, 11 only of our own patients were found to have developed gangrene during this period and, *without exception*, every one of these patients failed to follow treatment. This experience fits in with a fact well established with the older diets, namely, that it is the uncontrolled diabetic who is particularly susceptible to this complication.

The beneficial results with the high carbohydrate-low calorie diet in another cardiovascular disturbance, namely, coronary disease, were discussed elsewhere.¹ Our findings, clinically, and according to the electrocardiographic tracings, have been at times striking. We are not alone in this experience. Poulton² reported somewhat similar results. The explanation is not clear. My first impression was that improvement was due to supplying the heart muscle with that food which is essential for normal function, namely, glycogen. This would fit in with the suggestion made by Klotz that the media of the artery in a diabetic may degenerate prematurely because of lack of glycogen. Are the beneficial results due to reduction of lipoids in the intima?³ Does reduction of lipoids lead to more patent coronary arteries?³ The observations of Labbe and Heitz¹⁰ and of McMeans and Klotz⁵³ are of interest here. According to Labbe and Heitz¹⁰ deposition of cholesterol in the intima leads to obliteration of arteries, and McMeans and Klotz⁵³ have found that lipid deposits produced in the aorta of rabbits by feeding cholesterol *disappear* if the cholesterol is discontinued for several weeks.

Method of Investigation In order to determine whether the high carbohydrate-low calorie diet can prevent, or at least delay development of, arteriosclerosis, 50 diabetics who were treated with this diet were investigated. The cases were carefully selected with respect to the condition of the cardiovascular system, when these 50 patients were first given the new diet, they had no signs of arteriosclerosis according to (a) careful physical examination, (b) examination of the fundi, (c) roentgen-ray examination of the vessels of the lower extremities for calcification and (d) roentgen-ray examination of the heart (six foot plate).

Though, as stated, the juvenile diabetic apparently develops arteriosclerosis as readily as the adult, children were not included in this study. Since liability to arteriosclerosis increases with age even in nondiabetics, and since we are particularly concerned with arteriosclerosis in the young diabetic, all individuals past age 50 years were also excluded. A summary of the cases selected with respect to age, duration of diabetes, and severity of diabetes is shown in table 18. It will be observed that the maximum, minimum and average ages were 49, 29, 43.8 years respectively. The maximum, minimum and average durations of the diabetes were 8.3, 4.5 and 5.6 years respectively. Of these 50 diabetics, 16 required insulin and, in 34 cases, the diabetes could be controlled by diet alone. Different degrees of severity of diabetes were, therefore, also included.

Of these 50 individuals, arteriosclerotic changes were detected in 14 only, an incidence of 28 per cent. This incidence, it will be noted, is remarkably low when compared with our experiences with the older diets. In a similar age group of individuals and, according to the same methods of examination, cardiovascular disease was found in 55 per cent of the cases.² In calculating this percentage, however, no consideration was given to *duration* of the diabetes. The beneficial effects of the high carbohydrate-low calorie diet

TABLE XVIII

Summary 1

| | | | |
|----------------------|---------|-----|----|
| Number of cases | | | 50 |
| Age Maximum | 49 | | |
| Minimum | 29 | | |
| Average | 43.8 | | |
| Duration of diabetes | Maximum | 8.3 | |
| | Minimum | 4.5 | |
| | Average | 5.6 | |
| Insulin | | | 16 |
| No insulin | | | 34 |
| Arteriosclerosis | | | 14 |

are more clearly shown when consideration is given to the *durations of the diabetes*. As stated previously, very few diabetics, *regardless of age*, were found in the past to have escaped vascular disease when they had diabetes for five years or more, according to postmortem findings³ none escaped. In our previous study² of 81 individuals of 50 years of age and under who had diabetes for *five years or more*, 69—an incidence of about 85 per cent—had vascular disease, and even when the duration of the diabetes was less than five years, of 162 individuals of the same age group, 74—an incidence of about 40 per cent—were found to have vascular disease.

TABLE XIX

Relationship between Duration of Diabetes and Development of Arteriosclerosis

| Duration of Diabetes (Years) | Number of Cases | Arteriosclerosis | |
|------------------------------|-----------------|------------------|--------|
| | | Present | Absent |
| 4.0-4.5 | 13 | 2 | 11 |
| 4.6-5.0 | 9 | 1 | 8 |
| 5.1-5.5 | 10 | 3 | 7 |
| 5.6-6.0 | 6 | 3 | 3 |
| 6.1-6.5 | 1 | 0 | 1 |
| 6.6-7.0 | 5 | 1 | 4 |
| 7.1-7.5 | 3 | 2 | 1 |
| 7.6-8.0 | 1 | 0 | 1 |
| 8.1-8.5 | 2 | 2 | 0 |

In table 19 is shown in more detail the relationship found between duration of diabetes and development of cardiovascular disease in this group of 50 cases. It will be observed that of 28 individuals with the diabetes of more than five years' duration, cardiovascular disease was detected in only 11—an incidence of approximately 39.3 per cent, that is, less than one-half the incidence which was found among our control cases of a similar age group². It will be shown, however, presently that even this relatively low incidence can probably be lowered with proper attention to diet. Also significant appears to be the fact that some of these diabetics were treated with the older diets for periods ranging from six months to more than three years, *before* they were given the high carbohydrate-low calorie diet. In some, the blood cholesterol was not very high with the older diets. The data,

however, clearly show that a number of these patients were exposed to excess quantities of blood cholesterol for some time. Space does not permit citation of all the cases. The data in tables 20 and 21 are illustrative. It will be observed that in one case (table 20) the patient was on the older type of diet for about 10 months before the high carbohydrate-low calorie diet was given and in the other case (table 21) the older type of diet was in use for about four years. Incidentally, in the case shown in table 17, the patient

TABLE XX

Duration of Diabetes and Degree of Hypercholesterolemia before and since Treatment with
High Carbohydrate Low Calorie Diet
(Hosp No 6000/29 No arteriosclerosis)

| Date | Plasma Cholesterol (%) | Date | Plasma Cholesterol (%) |
|--------------|------------------------------|----------------|------------------------------|
| Oct 30, 1929 | 0.232 * | Oct 18, 1930 | 0.109 |
| Nov 9 | 0.370 | Nov 22 | 0.185 |
| 16 | 0.427 | Sept 18, 1931 | 0.134 |
| 23 | 0.387 | Dec 24 | 0.228 |
| 30 | 0.308 | March 26, 1932 | 0.138 |
| Dec 14 | 0.362 | Oct 1 | 0.143 |
| 28 | 0.333 | Nov 15 | 0.138 |
| Jan 25, 1930 | 0.256 | Dec 17 | 0.154 |
| March 1 | 0.238 | Jan 21, 1933 | 0.164 |
| 15 | 0.228 | Aug 26 | 0.222 |
| June 28 | 0.326 | Oct 2 | 0.151 |
| Aug 1 | 0.387 † | Jan 27, 1934 | 0.187 |
| Sept 2 | 0.315 | April 28 | 0.277 |
| 20 | 0.235 | May 30 | 0.137 |

* Low carbohydrate diet

† High carbohydrate diet

TABLE XXI

Duration of Diabetes and Degree of Hypercholesterolemia before and since Treatment with
High Carbohydrate Low Calorie Diet
(Hosp No 2044/26 No arteriosclerosis)

| Date | Plasma Cholesterol (%) | Date | Plasma Cholesterol (%) |
|----------------|------------------------------|----------------|------------------------------|
| April 28, 1926 | * | June 20, 1930 | 0.222 |
| Nov 13 | 0.387 | July 26 | 0.227 |
| 21 | 0.302 | Aug 23 | 0.177 |
| 23 | 0.302 | Oct 15 | 0.232 |
| Jan 19, 1929 | 0.347 | Nov 22 | 0.285 |
| Febr 2 | 0.222 | March 21, 1931 | 0.238 |
| 16 | 0.354 | July 4 | 0.208 |
| March 30 | 0.321 | Dec 12 | 0.200 |
| May 11 | 0.427 | Jan 6, 1932 | 0.157 |
| June 29 | 0.302 | May 6 | 0.185 |
| July 20 | 0.370 | June 7 | 0.173 |
| Dec 14 | 0.378 | Febr 1, 1933 | 0.315 |
| March 15, 1930 | 0.268 | April 15 | 0.208 |
| May 17 | † | Sept 1 | 0.174 |
| 31 | 0.244 | Dec 9 | 0.214 |

* Low carbohydrate diet

† High carbohydrate diet

was on the older type of diet for about 17 months before the new diet was given. In all three tables, the data clearly show that these patients were exposed, for some time, to excess quantities of blood cholesterol before they were given the new diet. In spite of such exposures, however, none of these three individuals had any signs of cardiovascular disease when last examined, though all had diabetes for more than five years. It would thus appear that the high carbohydrate-low calorie diet protected them from this disease in spite of previous treatment. This fits in with the previously mentioned findings of McMeans and Klotz⁵³ namely, the disappearance of lipid deposits in the aortae of rabbits when cholesterol feeding was discontinued.

Assuming that the high carbohydrate-low calorie diet was responsible for the low incidence of arteriosclerosis in this group of cases, an attempt was made to find the cause of the arteriosclerosis in those who developed it. As will presently be seen, excess blood cholesterol again appears to have been an influencing factor.

Duration of diabetes alone is not *entirely* excluded. This is shown in table 22, the average duration of the disease in the cases with cardiovascular disease was slightly greater than in those without vascular disease. The difference, however, appears to be small and, as will presently be shown, was not an important factor.

Severity of diabetes was considered. The data in table 22 suggest that

TABLE XXII

Summary 2

| | Arteriosclerosis | No Arteriosclerosis |
|------------------------------|------------------|------------------------|
| Number | 14 | 36 |
| Average age (years) | 46.9 | 42.6 |
| Insulin (No) | 5 | 11 |
| No insulin (No) | 9 | 25 |
| Duration of diabetes (years) | 6.05 | 5.42 |

this was not a very important factor, it will be observed that of the 16 individuals who required insulin, five were found to have developed arteriosclerosis—an incidence of 31.2 per cent—and of the 34 individuals in whom the diabetes could be controlled by diet alone, arteriosclerosis was detected in nine—an incidence of 26.5 per cent. In view of the small number of observations, limited significance can be attached to the differences noted between these percentages. Incidentally, the data suggest that insulin, per se, does not appreciably protect the diabetic against arteriosclerosis. Joslin has stressed the importance of insulin in children. No child, he states, treated with insulin from the onset of the diabetes was found to have arteriosclerosis⁵⁴. According to our data, however, as I shall presently show, it would appear that it is not the insulin, per se, which protects the diabetic from premature arteriosclerosis, but the control of the diabetes, the diabetic

under good control with diet alone is no more liable to arteriosclerosis than the one who requires insulin to control the disease

Since neither duration of the diabetes nor severity of the disease appeared to account alone for the arteriosclerosis in the 14 cases, an attempt was made to estimate the *control* of the diabetes. As previously stated, Shepardson found, and it has been a fairly general impression for some time, that the uncontrolled diabetic is particularly susceptible to arteriosclerosis. An impression, however, is not proof, and a difficulty was at once encountered, namely, the absence of a reasonably reliable quantitative index of control. Such arbitrary terms as *poor*, *fair*, *good*, etc are not satisfactory. The same term used in any two clinics may not be, and as a rule is not, strictly comparable. In one of our previous studies of blood cholesterol, control of diabetes was judged by frequency of glycosuria.²² This index, however, could not be applied to this study since, with the disease of long duration (years) very few diabetics examine their urines with the necessary frequency. The following standard was, therefore, devised. It will be observed that, with it, data of different clinics are reasonably comparable. Though it is a very approximate index only of control, its simplicity recommends it. It is, at least in my opinion, more quantitative than any standard used hitherto. Degree of control of diabetes was rated as follows

| Rating | Laboratory Findings |
|--------|---|
| 0 | Fasting blood sugar higher than 0.18 per cent, glycosuria in the fasting state and acetonuria |
| 1 | Glycosuria in the fasting state, but no acetonuria, or, in the absence of glycosuria, a fasting blood sugar higher than 0.18 per cent |
| 2 | Fasting blood sugar higher than normal, but less than 0.18 per cent |
| 3 | Fasting blood sugar normal |

The following case taken at random from our records is cited as an example of the calculations

| | Urine sugar | Urine acetone | Blood sugar per cent | Control Index |
|--------------|----------------|------------------|----------------------------|------------------|
| Jan 27, 1933 | + | 0 | 0.232 | 1 |
| March 1 | 0 | 0 | 0.166 | 2 |
| June 14 | 0 | 0 | 0.145 | 2 |
| Sept 3 | 0 | 0 | 0.240 | 1 |
| Dec 2 | 0 | 0 | 0.108 | 3 |
| May 4, 1934 | 0 | 0 | 0.087 | 3 |
| July 8 | 0 | 0 | 0.171 | 2 |
| Aug 14 | + | tr | 0.263 | 0 |
| Aug 21 | 0 | 0 | 0.133 | 2 |
| Nov 3 | 0 | 0 | 0.111 | 3 |
| | | | Average | 1.90 |

It will be observed that of 10 examinations in this case, the average control index was 1.90. This value, it should be noted, closely approximates conditions described above under rating No. 2. In other words, a rating of 1.9 implies that, as a rule, the patient was exposed to mild hyperglycemia only, glycosuria and marked hyperglycemia were uncommon. Acetonuria

must have been very uncommon. This, it will be noted, fits in, in general, with the actual data. The reliability of this method of measuring control of diabetes was, however, tested in the following manner.

In a previous investigation²² the cholesterol content of the blood plasma was found to be a reliable indication of the control of the diabetes. In order, therefore, to test the reliability of the control index, *average* control index was compared with *average* plasma cholesterol. A summary of 938 observations in 200 cases of diabetes is shown in table 23. The averages are graphically recorded in chart 2.

TABLE XXIII
Relationship between Control Index and Plasma Cholesterol

| (938 observations on 200 diabetics) | | | | | | | | |
|-------------------------------------|-----------------------|-----------------|--------------------|--------|------|----------|-------------|---------------------------|
| Group | Control Index (Range) | Number of Cases | Plasma Cholesterol | | | | | |
| | | | M | ρ | PEm | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
| 1 | -1.00 | 23 | 244* | 24.2 | 3.37 | | | |
| 2 | 1.01-1.50 | 34 | 239 | 36.5 | 4.13 | 5 | 5.3 | 0.96 |
| 3 | 1.51-2.00 | 39 | 222 | 44.8 | 4.82 | 17 | 6.3 | 2.7 |
| 4 | 2.01-2.50 | 64 | 198 | 37.3 | 3.10 | 24 | 5.7 | 4.2 |
| 5 | 2.51-3.00 | 40 | 191 | 40.3 | 4.28 | 7 | 5.3 | 1.3 |
| A | -1.00 | 23 | 244 | 24.2 | 3.37 | | | |
| B | 1.51-2.00 | 39 | 222 | 44.8 | 4.82 | 22 | 5.9 | 3.7 |
| C | 2.51-3.00 | 40 | 191 | 40.3 | 4.28 | 31 | 6.4 | 4.8 |

* Milligrams per 100 c c plasma

M = Mean

ρ = Standard deviation

PEm = Probable error of mean

Δ = Difference between means

PE Δ = Probable error of difference

It will be observed that the 200 cases are grouped according to the control index, and that in comparing differences of cholesterol among the different groups, the significance of each difference is judged by its probable error. Assuming that when the ratio of a difference to its probable error is less than 3, little or no significance is to be attached to the difference, no significant relationship was found between the control index and plasma cholesterol when the ranges used in grouping the cases, according to the control index, were narrow. A significant difference of cholesterol was found between two groups only, namely, between Groups 3 and 4 ($\Delta/PE\Delta = 4.2$). However, when wider ranges of the control index were used, a definite re-

relationship was found between control index and plasma cholesterol. It will be observed that by comparing Group A with Group B the ratio of the difference to its probable error was 3.7 and with Groups B and C it was 4.8. As will presently be shown, however, the above data, alone, do not properly reflect the reliability of the control index.

The above mentioned 200 cases were selected at random. In view,

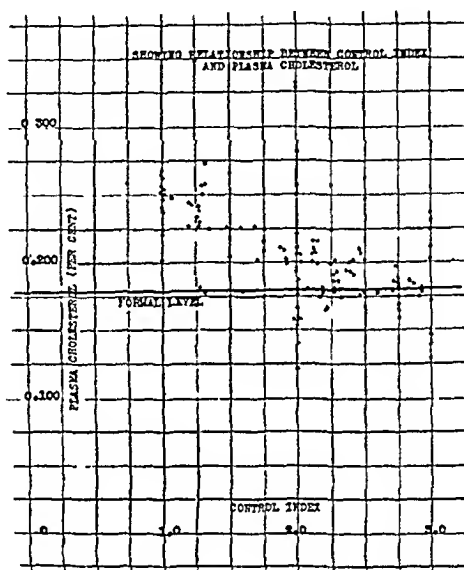


CHART 2

therefore, of the variety of conditions which may influence the level of the circulating cholesterol other than control of the diabetes, this method of estimating control of diabetes was reinvestigated and, in this investigation, cases which were found to have associated conditions or complications which could have influenced the cholesterol values were excluded. The results are summarized in table 24, and graphically recorded in chart 3. It will be observed that, by excluding conditions known to influence blood cholesterol other than the diabetes, a more definite relationship was found between control index and plasma cholesterol. (It may here be observed that a perfect correlation was not expected, since plasma cholesterol is, per se, not a perfect index of control of diabetes. Its use is, however, justified, the finding that blood cholesterol is a reliable index of the control of diabetes is statistically established.)

In previous studies, neither White and Hunt²⁰ nor I³⁸ were able to find a relationship between the height of blood sugar and the concentration of blood cholesterol. A priori, therefore, it would appear that no relationship should be found between control index and plasma cholesterol, since the control index is based to some extent upon blood sugar findings. Since a definite relationship was found, the discrepancy must be more apparent than

TABLE XXIV

Relationship between Control Index and Plasma Cholesterol in Uncomplicated Diabetes

(1037 observations on 187 diabetics)

| Group | Control Index (Range) | Number of Cases | Plasma Cholesterol | | | | | |
|-------|-----------------------|-----------------|--------------------|--------|------|----------|-------------|---------------------------|
| | | | M | ρ | PEm | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
| 1 | -1 00 | 23 | 277 | 58 | 8 10 | | | |
| 2 | 1 01-1 50 | 27 | 253 | 43 | 5 54 | 24 | 9 8 | 2 4 |
| 3 | 1 51-2 00 | 40 | 228 | 34 | 3 60 | 25 | 6 6 | 3 8 |
| 4 | 2 01-2 50 | 45 | 210 | 34 | 3 30 | 18 | 4 9 | 3 7 |
| 5 | 2 51-3 00 | 52 | 181 | 51 | 4 73 | 29 | 5 8 | 5 0 |
| A | -1 00 | 23 | 277 | 58 | 8 10 | | | |
| B | 1 51-2 00 | 40 | 228 | 34 | 3 60 | 49 | 8 9 | 5 5 |
| C | 2 51-3 00 | 52 | 181 | 51 | 4 73 | 47 | 5 9 | 7 9 |

* Milligrams per 100 c c plasma

M = Mean

 ρ = Standard deviation

PEm = Probable error of mean

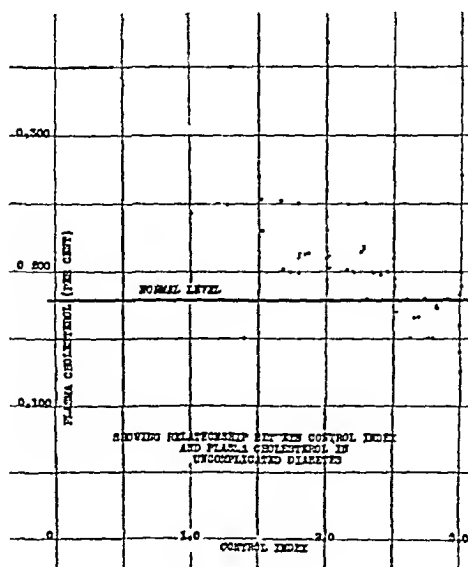
 Δ = Difference between meansPE Δ = Probable error of difference

CHART 3

real The explanation of the parallelism between the control index and plasma cholesterol is found in the method of calculating the control index It should be observed ^{25, 38} that in the attempt to relate blood sugar to blood cholesterol, *level* of cholesterol was compared with actual *level* of blood sugar, whereas, in calculating the control index, control of the diabetes is judged more by the *persistence* of high or low levels of blood sugar than by actual height, a blood sugar of 0.2 per cent, for example, has the same significance as a blood sugar of 0.3 per cent

TABLE XXV
Control of Diabetes

| Group | No | Number of Visits | Control Index |
|-----------------------|----|------------------|---------------|
| Whole | 50 | 819 | 1.94 |
| With arteriosclerosis | 14 | 253 | 1.53 |
| No arteriosclerosis | 36 | 566 | 2.12 |

In table 25 is shown the relationship found between the control index and cardiovascular disease in the 50 cases investigated It will be observed that of 253 examinations in the 14 cases with cardiovascular disease, the average control index was 1.53, whereas, of 566 examinations in the 36 cases with no cardiovascular disease, the average control index was 2.12 Therefore, from these data alone, it would appear that poor control of the diabetes was an important cause of the cardiovascular disease in these 14 cases It should be observed that a control index of 1.53 implies, according to the above mentioned method of rating, that, as a rule, the patient was exposed to marked hyperglycemia, the blood sugar, as a rule, was higher than 0.18 per cent Glycosuria was also frequent

TABLE XXVI
Control of Diabetes

| Group | Arteriosclerosis | | | | | | | No Arteriosclerosis | | | | | | |
|------------|------------------|--------|---------------------|-----|----|----|------|---------------------|--------|---------------------|-----|-----|-----|------|
| | No | Visits | Control of Diabetes | | | | | No | Visits | Control of Diabetes | | | | |
| | | | 0 | 1 | 2 | 3 | A M | | | 0 | 1 | 2 | 3 | A M |
| Whole | 14 | 253 | 9 | 129 | 87 | 28 | 1.53 | 36 | 566 | 6 | .71 | 338 | 151 | 2.12 |
| Insulin | 5 | 121 | 6 | 71 | 35 | 9 | 1.41 | 11 | 206 | 3 | .52 | 122 | 29 | 1.86 |
| No insulin | 9 | 132 | 3 | 58 | 52 | 19 | 1.66 | 25 | 360 | 3 | .19 | 216 | 121 | 2.26 |

It is obviously more difficult to control the diabetes when it is severe than when it is mild Therefore, in order to measure the effects of severity of the diabetes, the cases were regrouped and the average control index of the insulin-treated cases was compared with the average control index of the in-

dividuals in whom the diabetes could be controlled by diet alone. A summary of the findings is shown in table 26. It will be observed that severity of the diabetes was to some extent an influencing factor, in both groups, the average control index of the insulin-treated cases was somewhat lower than that of the individuals in whom the diabetes could be controlled by diet alone. The data, however, also show that, *regardless of the severity of the disease*, the average control index of those with cardiovascular disease was lower than in the group of cases with no cardiovascular disease. These findings, therefore, fit in with and tend to confirm the previous observation that severity of diabetes does not alone explain the development of the cardiovascular disease in these cases. They also support another observation made previously, namely, that insulin, per se, does not protect the diabetic against cardiovascular disease.

TABLE XXVII

Relationship between Plasma Cholesterol and Cardiovascular Disease in 50 Diabetics Treated with the High Carbohydrate-Low Calorie Diet

| Group | No | Plasma Cholesterol | | | | | |
|---------------------------|------|--------------------|--------|------|----------|-------------|---------------------------|
| | | M | ρ | PEm | Δ | PE Δ | $\frac{\Delta}{PE\Delta}$ |
| Whole | 819* | 202 | | | | | |
| Cardiovascular disease | 253 | 220 | 76 | 3.18 | 25 | 4.1 | 6.1 |
| No cardiovascular disease | 566 | 195 | 89 | 2.59 | | | |

M = Mean

ρ = Standard deviation

PEm = Probable error of mean

Δ = Difference between means

PE Δ = Probable error of difference

Table 27 shows the relationship found between plasma cholesterol and cardiovascular disease in this group of 50 cases. The data fit in with the previous studies (see table 13). It will be observed that the average plasma cholesterol in the cases with cardiovascular disease was higher than among the individuals with no detectable vascular disturbances, of 253 tests among the arteriosclerotics, the average cholesterol was 0.22 per cent, whereas, of 566 tests among those with no detectable signs of arteriosclerosis, the average cholesterol was 0.195 per cent only. The difference between the two groups is not very great, namely, 25 milligrams, but the ratio of the difference to its probable error (6.1) clearly indicates that the difference was significant.

Table 28 shows the relationship found between the control index and plasma cholesterol in these 50 cases grouped according to severity of the disease. Both control index and cholesterol also clearly show the relation-

TABLE XXVIII

Relationship between Control Index and Plasma Cholesterol in 50 Diabetics Treated with High Carbohydrate Low Calorie Diet
(Effects of insulin)

| Group | Arteriosclerosis | | | | No Arteriosclerosis | | | |
|------------|------------------|------------------|---------------|-----------------|---------------------|------------------|---------------|-----------------|
| | Number of Cases | Number of Visits | Control Index | Cholesterol (%) | Number of Cases | Number of Visits | Control Index | Cholesterol (%) |
| Whole | 14 | 253 | 1 53 | 0 220 | 36 | 566 | 1 86 | 0 195 |
| Insulin | 5 | 121 | 1 41 | 0 228 | 11 | 206 | 2 26 | 0 201 |
| No insulin | 9 | 132 | 1 66 | 0 204 | 25 | 360 | 2 12 | 0 191 |

ship between control of the diabetes and development of cardiovascular disease. It will be observed that the average cholesterol was higher and the average control index was lower among those with cardiovascular disease and among those in whom there were no signs of cardiovascular disease. This applied to the insulin-treated cases as well as to those in whom the diabetes could be controlled by diet alone. Since in the selection of these cases, care was taken to exclude conditions which are known to affect blood cholesterol, the higher average of cholesterol found among the cases with cardiovascular disease is reasonably attributed to dietary irregularities.

Tables 29 and 30 show the relationship between control of diabetes, plasma cholesterol, duration of diabetes and arteriosclerosis. The data

TABLE XXIX

Relationship between Degree of Control of Diabetes, Duration of Diabetes and Development of Arteriosclerosis

| Duration of Diabetes (Years) | Arteriosclerosis | | | | | | | No Arteriosclerosis | | | | | | |
|------------------------------|------------------|---------------------|---|-----|----|----|------|---------------------|---------------------|---|----|-----|-----|------|
| | Number of Cases | Control of Diabetes | | | | | | Number of Cases | Control of Diabetes | | | | | |
| | | Number of Tests | 0 | 1 | 2 | 3 | M | | Number of Tests | 0 | 1 | 2 | 3 | M |
| 4 0-4 5 | 2 | 36 | 4 | 3 | 27 | 2 | 1 75 | 11 | 132 | 2 | 18 | 88 | 24 | 2 01 |
| 4 6-5 0 | 1 | 13 | 0 | 8 | 4 | 1 | 1 46 | 8 | 126 | 0 | 13 | 66 | 47 | 2 26 |
| 5 1-5 5 | 3 | 38 | 1 | 19 | 13 | 5 | 1 56 | 7 | 122 | 2 | 11 | 68 | 41 | 2 21 |
| 5 6-6 0 | 3 | 46 | 0 | 24 | 19 | 3 | 1 54 | 3 | 51 | 0 | 13 | 27 | 11 | 1 96 |
| 6 1-6 5 | | | | | | | | 1 | 17 | 0 | 2 | 7 | 8 | 2 35 |
| 6 6-7 0 | 1 | 20 | 1 | 14 | 2 | 3 | 1 35 | 4 | 73 | 1 | 9 | 51 | 12 | 2 01 |
| 7 1-7 5 | 2 | 63 | 2 | 42 | 8 | 11 | 1 44 | 1 | 26 | 0 | 3 | 17 | 6 | 2 11 |
| 7 6-8 0 | | | | | | | | 1 | 19 | 1 | 2 | 14 | 2 | 1 90 |
| 8 1-8 5 | 2 | 37 | 1 | 19 | 14 | 3 | 1 51 | | | | | | | |
| Summary | 14 | 253 | 9 | 129 | 87 | 28 | 1 53 | 36 | 566 | 6 | 71 | 338 | 151 | 2 12 |

TABLE XXX

Relationship between Plasma Cholesterol, Duration of Diabetes and Development of Arteriosclerosis

| Duration of Diabetes (Years) | Arteriosclerosis | | | | | No Arteriosclerosis | | | | |
|------------------------------|------------------|-------------------------------|---------|---------|---------|---------------------|-------------------------------|---------|---------|---------|
| | Number of Cases | Plasma Cholesterol (Per Cent) | | | | Number of Cases | Plasma Cholesterol (Per Cent) | | | |
| | | Number of Tests | Maximum | Minimum | Average | | Number of Tests | Maximum | Minimum | Average |
| 4 0-4 5 | 2 | 36 | 0 241 | 0 151 | 0 212 | 11 | 132 | 0 277 | 0 111 | 0 201 |
| 4 6-5 0 | 1 | 13 | 0 189 | 0 111 | 0 198 | 8 | 126 | 0 297 | 0 120 | 0 189 |
| 5 1-5 5 | 3 | 38 | 0 315 | 0 124 | 0 229 | 7 | 122 | 0 333 | 0 133 | 0 193 |
| 5 6-6 0 | 3 | 46 | 0 252 | 0 133 | 0 234 | 3 | 51 | 0 252 | 0 166 | 0 187 |
| 6 1-6 5 | | | | | | 1 | 17 | 0 241 | 0 141 | 0 198 |
| 6 6-7 0 | 1 | 20 | 0 244 | 0 181 | 0 230 | 4 | 73 | 0 282 | 0 132 | 0 200 |
| 7 1-7 5 | 2 | 63 | 0 333 | 0 171 | 0 215 | 1 | 26 | 0 264 | 0 154 | 0 213 |
| 7 6-8 0 | | | | | | 1 | 19 | 0 222 | 0 100 | 0 202 |
| 8 1-8 5 | 2 | 37 | 0 268 | 0 159 | 0 224 | | | | | |
| Summary | 14 | 253 | 0 333 | 0 111 | 0 220 | 36 | 566 | 0 333 | 0 100 | 0 195 |

clearly show that the important influencing factor in the development of the arteriosclerosis in these 14 cases was poor control of the diabetes, as contrasted with previous methods of treatment, duration of the diabetes does not appear to have been an important factor. It will be noted that there were 28 individuals who had diabetes for more than five years and that 11 of these 28 were found to have cardiovascular disease when last examined. Though this incidence is very low compared with previous experiences with diabetes of the same duration, the probability is that it would have been still lower had these 11 people followed treatment carefully. It will be observed that compared with the 17 patients who did not develop cardiovascular disease, the average cholesterol was high and the control index was low.

SUMMARY

Combining all of the above experiences, it appears reasonable to conclude that excess blood cholesterol is an important etiological factor in the production of arteriosclerosis in the young diabetic. The data also appear to indicate that treatment with the high carbohydrate-low calorie diet has delayed development of cardiovascular disease in the cases investigated. Time alone and further studies will determine whether this diet can actually *prevent* premature development of this complication.

The findings in these 50 cases of diabetes are reported *in detail* for a definite reason. I believe I have clearly shown elsewhere that one of the most constant characteristics of the high carbohydrate-low calorie diet is an immediate and sustained decrease of plasma cholesterol. I believe this

finding is incontestable. Therefore, if the conclusion that excess cholesterol in the blood causes cardiovascular disease in the young diabetic is also found to be correct, the outlook of the diabetic has been greatly improved. Repetition of these studies is, therefore, warranted by others with similarly available facilities. In order, however, that other data may be comparable with our own, the method of investigation should be the same, the *combined* method of detecting arteriosclerosis should be used in *every* case. This includes, as previously stated, a *very careful* general physical examination, examination of the fundi, roentgen-ray examination of the lower extremities for calcification of the arteries and roentgen-ray examination (six foot plate) of the heart. As we have shown previously² any one method alone or any combination of two or three methods alone, does not afford a sufficiently reliable index of the presence, or absence, of arteriosclerosis. For the estimation of plasma cholesterol, *all blood samples should be collected in the fasting state*, and in the interpretation of cholesterol data, all conditions known to affect the concentration of cholesterol in the blood—that is, whether they increase or decrease it—other than diabetes and arteriosclerosis should be excluded as much as possible. In order that data of different clinics with respect to degree of control of diabetes may be reasonably comparable, it is also suggested that the control index reported here should be used. It appears to be a reasonably quantitative measure of control of diabetes from a statistical point of view. It is, at least, more reliable than use of such terms as good, fair, poor, etc. Finally, in interpreting blood cholesterol, differences noted should be judged by their *probable errors*.

I wish to take this opportunity of expressing my thanks to Dr C A Peters, recently retired Chief of one of the Medical Services of this hospital, to Dr A H Gordon and Dr C P Howard, Chiefs of the Medical Services, who were, with very few exceptions only, responsible for all of the physical examinations, to Dr S H McKee, Chief of the Department of Ophthalmology, who made all fundi examinations, to Dr W L Ritchie, Director of the Department of Roentgenology, for the liberal use of his time in the interpretation of the roentgen-ray findings, to Dr A F Fowler and Dr E H Bensley for their assistance in the management of these cases in the wards, to Dr Neil Feeney for his clinical examinations of the out-door cases to be reported upon later, to Misses Eleanor V Bazin, Marjorie Mountford and Eileen Payette for the careful attention to details in the necessary collection and assortment of data, and to Dr L J Rhea, our Pathologist, for his cooperation throughout this investigation.

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ELECTROCARDIOGRAPHIC STUDIES IN ACUTE CORONARY THROMBOSIS

I TRANSIENT HEART BLOCK OF ALL GRADES IN A T₃, Q₃ TYPE OF CASE, WITH SERIAL ELECTROCARDIOGRAMS FROM ACTUAL ONSET TO AND AFTER CLINICAL RECOVERY *

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MUCH that is known concerning the electrocardiogram of acute coronary thrombosis has been deduced from the study of records made at various stages of the patient's illness and from short—often disappointingly short—serials. Smith's¹ animal experiments showed in a general way what might be expected. Herrick,^{2,3} Pardee,^{4,5,6} Rothschild, Mann and Oppenheimer,⁷ Levine,⁸ and others, contributed importantly to the development of the present knowledge of electrocardiographic changes. Parkinson and Bedford⁹ in 1928 contributed magnificently in their study of 28 cases. Their study not only summarized everything of importance that had previously been brought out, but they described in a more detailed manner than had previously been attempted transitions of the form of the ventricular complexes as they occur through the course of coronary occlusion, illustrating most of these mutations with electrocardiograms from their patients, and supplementing the information so given by the publication of a schematic illustration showing their concept of the general trend of such changes.

When Herrick, in 1919, published the first electrocardiogram from a case of acute coronary thrombosis the electrocardiograph was a stationary instrument, delicate, temperamental, and difficult of operation as those who have had experience with the instrument of those days will not fail to remember. At the onset and during the critical early stages of acute coronary occlusion conveyance of the patient to a place where an electrocardiogram could be recorded was interdicted by reason of the gravity of the patient's condition. Medical leaders such as Christian,¹⁰ as recently as 1925 felt constrained to advise "the obtaining of the electrocardiogram involves transportation of the patient, postpone it until the patient's condition has greatly improved, for rest is more important to the patient than an electrocardiogram. A live patient with a probable diagnosis of cardiac infarction is by far preferable to a dead one, definitely diagnosed by finding a typical electrocardiogram and the moving of the patient may make the difference between recovery and death."

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The evolution of the electrocardiograph to its present state of simplification of operation, reliability and adaptation to bedside use has made it practical without injury to the patient to study every phase of electrocardiographic mutation in acute coronary occlusion provided that we refrain from causing the patient to move except for the slight passive motion of the limbs incidental to application of the electrodes. Herrick¹¹ has called attention to the need of more detailed studies. No cogent reason remains why they should not be made in the three standard leads, and such studies should help immeasurably to clear up many muted questions concerning diagnosis, prognosis, localization and treatment. As to direct chest leads, although they have undoubtedly proved informative one is inclined to feel somewhat as Christian did in 1925. The application of electrodes for the chest leads involves moving the trunk of the patient. Only in selected cases without evidences of shock does this seem justified.

In view of the circumstances as outlined above it is to be considered a credit to the medical profession at large that no detailed serial electrocardiograms were made until the evolution of a new type of electrocardiograph made it practical to do so with safety to the patient. Thus Gilchrist and Ritchie¹² in April 1930, after making a survey of the literature noted the discrepancy between the immense volume of literature and the small number of cases reported in detail, remarking that "not until serial electrocardiograms became available was the electrocardiographic evidence of myocardial infarction placed on a satisfactory basis."

According to the writer's concept of what is possible with modern electrocardiographic apparatus there are less than a score of serial electrocardiograms in the literature which show sufficient detail—in at least a portion of the progress of average cases of acute coronary thrombosis—to permit of satisfactory analysis of the probable underlying pathology stage by stage. The T₁ case reported in 1929 by Moore and Campbell¹³ remains the only case of acute coronary occlusion reported in detailed serial electrocardiograms from the date of actual onset to and beyond the date of clinical recovery, showing transition of the ventricular complexes as described by Parkinson and Bedford.

This is not to say that other good serials have not been published but rather, that in some instances, intervals between taking of graphs have been so long as to cause the omission of important mutations and changes of rhythm, and in others that so much time elapsed from the onset until the first electrocardiogram was recorded that all of the early transitions were missed. Such as they are, however, the serials now on record do show that a definite order of mutation of the ventricular complexes generally but not invariably occurs in the manner outlined by Parkinson and Bedford, and that most of the cases can be separated into one of the two classes described by them as T₁ and T₂ types. In a minority of cases the appearance of atypical or bizarre forms of ventricular complexes confuses the diagnosis, in

coronary occlusion but, although the clinical picture is that of a case of recent acute coronary occlusion, there is failure on the part of the ventricular complexes to go through the typical stages of mutation of form

The occasional failure of the electrocardiograph to record any diagnostic changes at the onset of acute coronary occlusion has been discussed by many writers. Wolferth,^{14, 15} Wood,^{16, 17} and co-workers have shown that in such cases (a) chest leads often clinch the diagnosis, (b) the greatest usefulness of chest leads is in T_1 cases since diagnostic changes usually occur in the standard leads in T_2 cases, (c) rarely both standard and direct chest leads fail to show diagnostic changes at the onset. It is to be observed in this connection that most of the cases reported in the literature purporting to show failure of the electrocardiogram to record diagnostic changes have been without the benefit of detailed serial electrocardiographic studies.

The case to be reported is one of a series of case studies in acute coronary thrombosis in which it was attempted to secure more detailed electrocardiographic serials than have previously been reported in a series of cases, the purpose being to add to the small number of satisfactory serials thus far published, thus increasing the material available for study and perhaps eventual solution of some of the problems previously referred to.

CASE REPORT

WRGH, white male, aged 58. At 11 30 a.m. on December 7, 1932, he complained of symptoms of indigestion similar in character to attacks he had experienced off and on for 25 years. The heart sounds were clearly heard. The blood pressure was 158 millimeters of mercury systolic and 85 diastolic. He had no precordial pain at this time. The patient had led an active life. Polo playing was one of his favorite diversions. Except for "spells of indigestion with colicky abdominal pain" and a lifetime of constipation he had never been ill. His symptoms were relieved but returned late in the afternoon and hospitalization was advised.

Though he now felt well he consented to go to the hospital, laughing and joking in the automobile while en route, and was admitted at 6 10 p.m. At 6 55 p.m. he experienced the onset of extremely severe precordial pain, went into collapse and almost died. Heroic stimulation with caffeine sodiobenzoate and intravenous 50 per cent glucose revived him but he still looked exceedingly ill. The first electrocardiogram was made at the height of the attack while stimulants were being administered. A blood pressure reading could not be made at this time because of the pressing urgency of the emergency, but the patient was pulseless at the radial, brachial and femoral arteries, and heart sounds could barely be made out. The blood pressure, 30 minutes later, was 80 systolic and 50 diastolic. Other symptoms were blue-black cyanosis of the lips, dusky gray cyanosis of the skin, profound weakness, shock, profuse cold perspiration, restlessness and Cheyne-Stokes respiration.

Physical examination, after the acuteness of the attack had passed away, showed weak heart sounds, no murmurs, pulse feeble but regular at the right radial, no pulse at left radial (patient stated that this had always been absent). A few scattered moist râles were heard at the bases. Pain lasted 20 hours. It started over the precordium radiating to a point in the back between the scapulae. After the first few days the pain between the scapulae was more severe than the anterior pain, and as pain gradually subsided it was from this posterior point that it was last to disappear. During the first few days pain was also felt in both arms and forearms, and in the epigastrium.

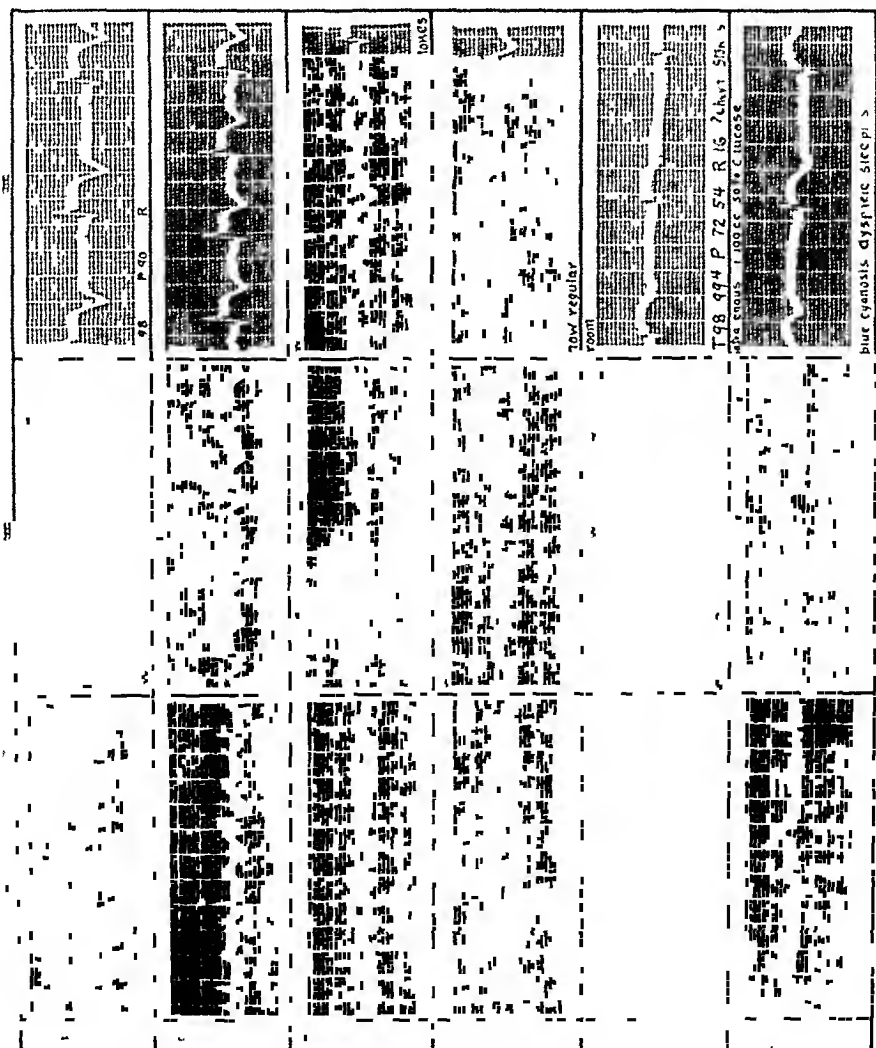


Fig 1 Onset of acute coronary thrombosis to third day (The electrocardiograms illustrated in this and in all of the succeeding plates were recorded without overshooting by means of a standard, mobile, string galvanometer Deflections of 1cm-lmv In the interest of conservation of space the graphs have been photographically reduced approximately 40 per cent)

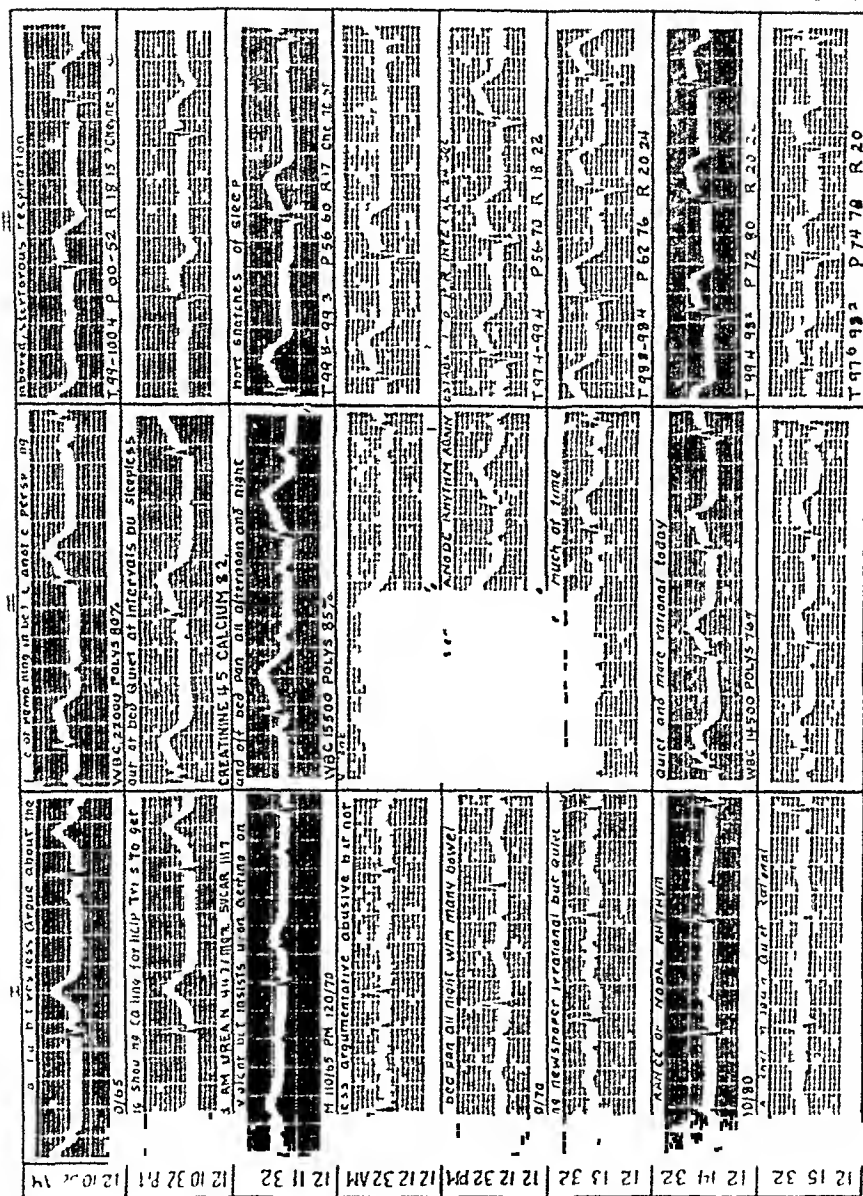


FIG 2 Fourth to ninth days

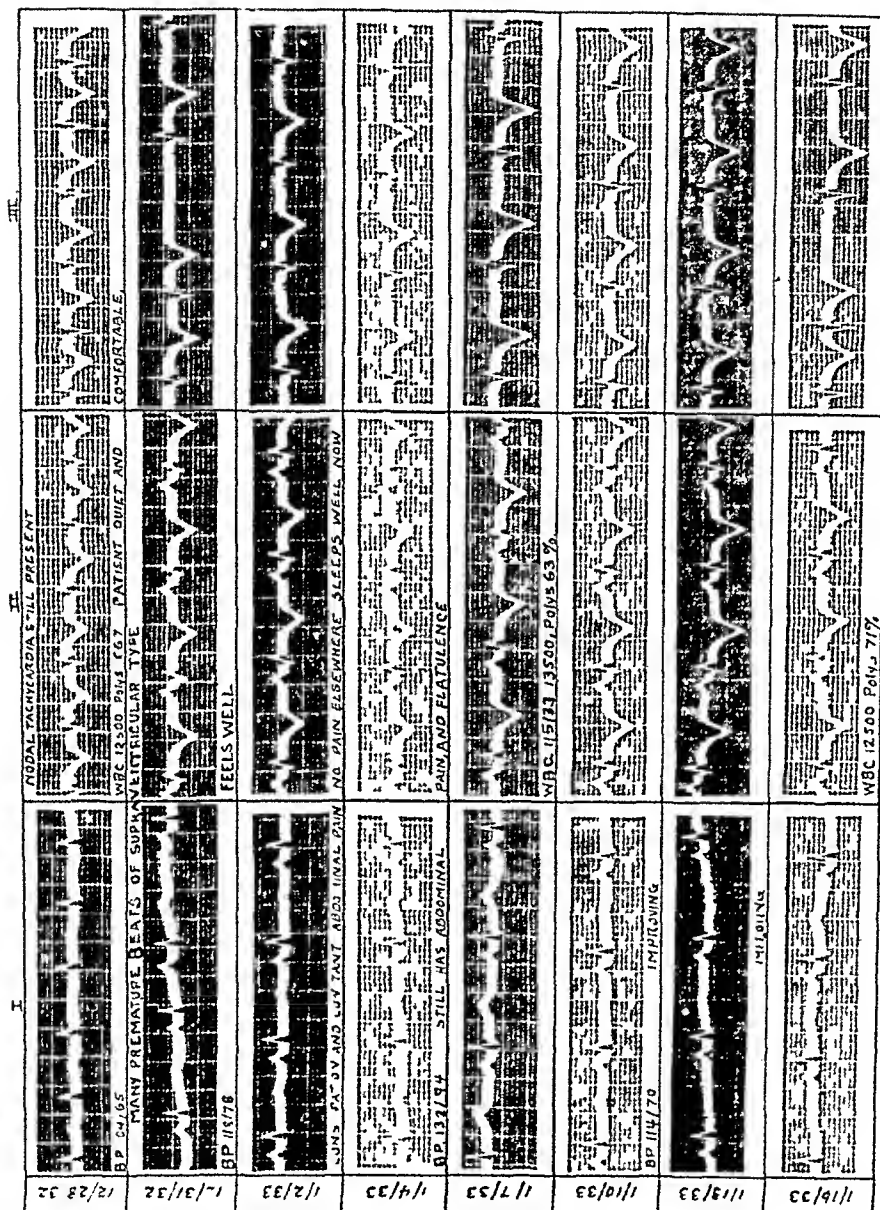


FIG 4 Twenty-second to forty-first days

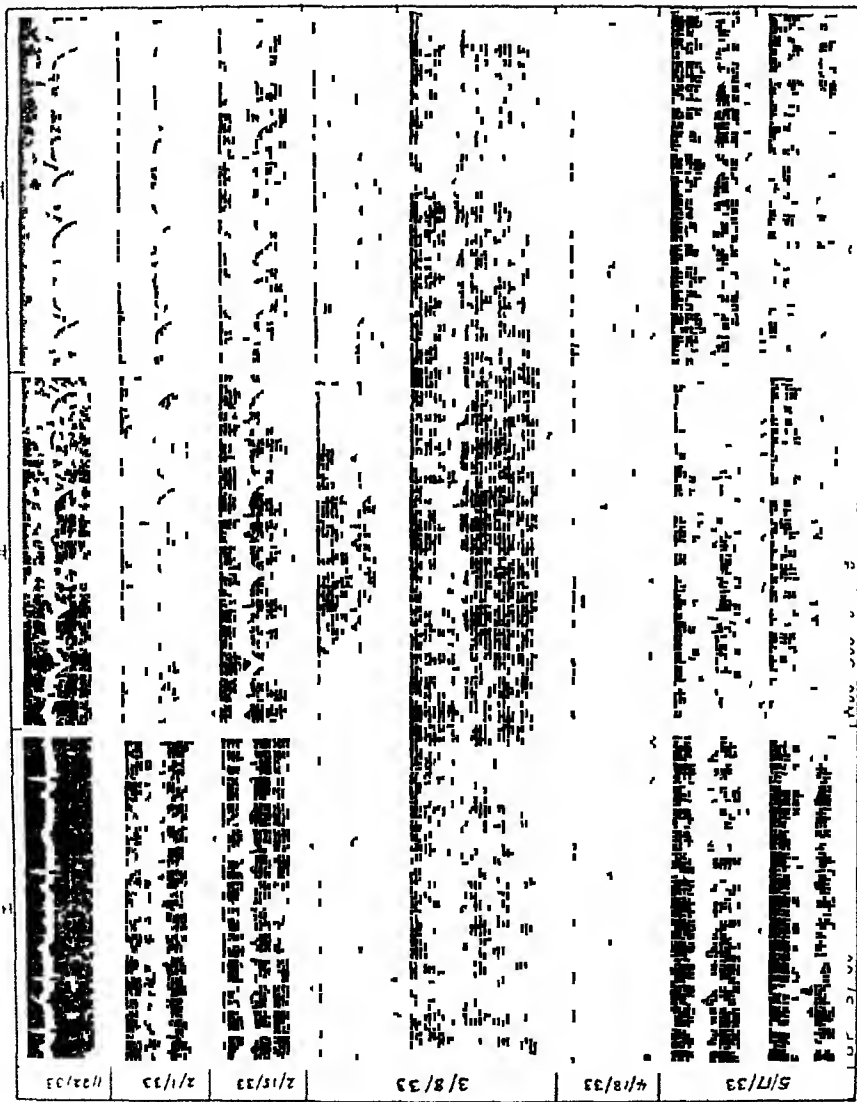


FIG 5 Forty-seventh to one hundred sixty-second days

Twelve graphs were recorded during this period. As electrocardiographic mutations are very slow during the stage of recovery, six of the records were omitted from this plate. In common with the graphs illustrated, they show how greatly the frequency of incidence of premature beats has increased during this stage. In this plate the record of 3-8-33 shows Lead IV in addition to the standard leads. This was recorded by means of direct chest leads according to the method of Wolferth and Wood. The patient is still living and active more than 7 year (June 1934) after the first electrocardiogram was recorded.

Blood pressure A study of the blood pressure as recorded at annual physical examinations since 1918 showed that it had been within normal range until 1925. Thereafter there had been an annual rise, reaching 164 systolic and 100 diastolic in January 1930. From this time on the blood pressure was elevated. A few days before the onset it was 165 systolic and 85 diastolic. The effect of the thrombosis was a precipitous drop of blood pressure to nil as evidenced by the condition of the patient as described above. From the onset to March 1933 the blood pressure level was always distinctly less than it had been during a period of five years preceding the attack. After March the blood pressure gradually increased. Six months after the onset of coronary occlusion it registered 175 systolic and 100 diastolic. The systolic level at this point was greater than had ever been recorded in this patient over a period of 16 years.

Temperature This was recorded every four hours during the febrile period. It was normal on admission, gradually ascending to reach a peak of 100.6° on the fifth day, then gradually and irregularly descending to return to the normal level on the twenty-third day.

Leukocytes 22,000 at onset, dropping to 18,000 the third day, and returning to 22,000 on the fourth day during the second acute collapse. From the latter point the count gradually dropped, reaching 7500 the nineteenth day, then had a secondary ascent to between 11,500 and 13,000 until February, but was normal thereafter.

Course No case hitherto reported in the literature has had a course as violent. Restless from the onset, the patient became tremendously violent again and again. This physical activity continued despite the constant day and night efforts of special nurses and attendants until the sixth day. During this period the patient was exceedingly abusive, restless and irritable. Whenever possible he kicked at attendants and on one occasion struck at an attending physician with enough force to throw him halfway across the room. At this time he did not seem to be sufficiently well oriented to identify individuals. Following this came a period of two weeks during which the patient insisted upon getting up and about, attempting to accomplish by argument and "logic" what he had formerly attempted by violence. The last unreasonable spell occurred on the twenty-first day when he sat up in bed against orders, and threatened to get out of bed. The results were sufficient to quell the last notions of physical resistance which the patient entertained, as a nodal tachycardia promptly ensued and lasted for 24 hours causing him to feel as "weak as a kitten". During January he had the most extraordinary amount of intestinal flatulence, with the constant desire to relieve it by means of enemas. There were days when he seemed to be on the bed p in nearly all the time, with inadequate results. This trouble gradually lessened but, even when able, later on, to be up and about, and since leaving the hospital, constipation and intestinal flatulence have been a difficult problem for him.

Electrocardiograms The first graph of December 7, 1932, taken at the onset of the attack, shows depression of the R-T segment in Lead I with elevation of R-T segments in Leads II and III. Take-off of T is direct from the descending limbs of R-waves in Leads II and III. T-waves have an upward convexity above the base line in Leads II and III followed by a downward projection of about equal amplitude extending as a pointed tip below the isoelectric level. Q_1 is well developed and of the type which Pardee¹⁸ considers significant. Another graph the same day and two the following day showed much the same characteristics except that reduction of amplitude of QRS developed rapidly. After this there was a period of eight days during which the T-waves of Leads II and III became sharply convex, upright waves with take-off ascending the R-wave, losing their negative projections. At the same time T_1 became altered. It became greater in height and breadth until the fourth day. Then it lost amplitude rapidly and the Q-waves in Leads II and III became especially well developed. In the latter lead they were at times the tallest deflections of QRS to be found in any lead. On the tenth day small negative projections of T again ap-

peared in Leads II and III. From that date forward the T-waves in these two leads gradually increased in depth below the isoelectric level until, on the thirty-second day their point of maximum inversion was reached. After that they gradually diminished in depth from graph to graph. The amplitude of QRS never returned to anything approaching that found in the first record, and the deep Q_3 waves, still of the significant type appear to have become a permanent fixture.

Rhythm. The P-R interval in the two graphs of the day of onset was 16 second. By the next morning it measured 23 second, and that afternoon complete heart block was established. At this time the rhythm was absolutely regular, but several hours before, second degree heart block with dropped beats* had been noted by clinical observation. Complete heart block was present without intermission during the third, fourth and fifth days. Although the ventricles were rhythmic and slow, the rate of the auricles during this period was, for a time, nearly as slow and there was noted a rhythmic waxing and waning of the amplitude of the P-waves. Only sections showing sizeable P-waves were included in the serial shown in the plates in order that the daily progress of the abnormal rhythm might better be visualized. Hundreds of feet of electrocardiogram were recorded during the three days when complete heart block was present. Much of this record showed a waxing and waning of amplitude of the P-waves as described, but there was no irregularity of rhythm of the ventricle, no relation between incidence of auricular and ventricular waves, and no wandering of the auricular pacemaker.

On the morning of the sixth day second and first degree heart block were present, the former predominating. The section in the serial from Lead I was inserted to show an interval of prolongation of A-V conduction time only while sections from Leads II and III were cut to show the predominant second degree heart block. Normal sinus rhythm was more permanently established the same afternoon but with prolonged conduction time. This lasted only 24 hours when nodal rhythm with slow retrograde conduction to the auricles appeared. The next day sinus node rhythm was reestablished, with normal P-R interval. This continued until the afternoon of the twenty-first day when nodal tachycardia suddenly appeared after the patient sat up in bed against orders. This persisted about 24 hours. It was terminated by the use of quinidine. Following this, sinus node rhythm prevailed but premature beats were frequent. In the last graph made on the one hundred sixty-second day many premature beats from supraventricular and ventricular foci were recorded.

COMMENT

The principal clinical happenings have been noted on the plates illustrating the serial electrocardiograms and for sake of further convenience have been summarized in table 1. If the reader will follow them it will be observed that close clinical-electrocardiographic correlations can be studied from the actual onset and mutations of the graphs from stage to stage are so gradual that it is possible to compare these changes with the schematic concept of what such transitions should be as formulated by Parkinson and Bedford.

At the onset marked elevation of the R-T segments is recorded in Leads II and III and opposing such elevations there is slight but definite S-T depression in Lead I. According to the schematic concept R-T, S-T take-off

*Further examination of the long record of that morning revealed the presence of a single dropped beat due to momentary second degree heart block. Throughout the remainder of the graph first degree heart block with P-R interval constant at 23 second is recorded.

TABLE I

| Day | Rhythm | Ventricular Complexes in Lead III | Clinical Correlations |
|---------|--|--|--|
| 1 | Of S-A node origin No heart block No premature beats | T diphasic R-T take off high, halfway up R-waves QRS amplitude less than normal, but greater than later on | Some struggling but quiet as compared with succeeding days |
| 2 | First, second, third degree heart block in succession | T diphasic Amplitude of QRS diminishing Take-off of R-T from higher point of R-waves | Struggling constantly Extremely violent Maximum drop of blood pressure |
| 3, 4, 5 | Complete heart block, A-V ratio varying from 86 53, third day to 102 47, fifth day | T diphasic, changing on fifth day to monophasic QRS low amplitude R-T take-off maintained at higher level | Perpetual struggling, day and night |
| 6 | Second, then first degree heart block | T decidedly monophasic QRS amplitude diminishing R-T take-off higher | Less struggling Mostly quiet Worn out |
| 7 | S-A node rhythm No heart block | Same but very high arched T-waves | Sleeping |
| 8 | Nodal rhythm onset S-A block, 2 cycles, followed by ventricular escape | Height of R-T take off above base line diminishing | Quiet most of time |
| 9 | S-A node rhythm | Same Q ₃ very deep | Quiet |
| 10 | S-A node rhythm | T slightly diphasic R-T elevation diminishing | Quiet Temperature peak next day |
| 15 | S-A rhythm | R-T level isoelectric T ₃ all inverted | Quiet |
| 21 | S A rhythm changing in p m to nodal tachycardia | T less deeply inverted with tachycardia in p m | Unreasonably sitting up Momentary BP drop |
| 22 | Nodal tachycardia | No change | Quiet |
| 25 | S-A node rhythm with nodal premature beats | QRS amplitude very low | Quiet |
| 32 | S-A rhythm | Point of maximum inversion of T ₃ | Quiet |
| 163 | S-A node rhythm with nodal and ventricular premature beats | Very low amplitude QRS Permanent deep Q ₃ T ₂ and T ₃ still inverted | 2 mos out of hospital No cardiac symptoms Unwisely overactive |

should gradually approach the isoelectric thereafter, but the reverse is true here. The two graphs made on the day of onset show the R-T take-off about half-way up on the descending limb of R₃. The level of take-off is higher next day, and on the succeeding four days becomes still more elevated. It is not until the eighth day that the opposite trend is manifested. Thereafter gradual descent is illustrated, the isoelectric level being reached on the fifteenth day.

Transitions of the form of the T-waves also occur at first in reverse order. At the onset, in Leads II and III the T-waves have positive followed by negative deflections of about equal degree while the low take-off of T_1 gives it a somewhat stilted upright appearance. From this point onward the negative tip of the T_1 wave becomes less and less conspicuous until, by the fifth day, it is gone and we see what Parkinson and Bedford described as a "monophasic" curve of the ventricular complexes. Following still further the upward bowing of this curve, or the amplitude of T_3 if we so prefer to refer to it, becomes more and more sharply marked reaching a peak of amplitude on the seventh day. From this point onward the course of electrocardiographic events definitely follows the schematic concept of Parkinson and Bedford. The suggestion of a negative projection of T_1 again occurs on the tenth day, it is definite on the eleventh day, then on the fifteenth day *all* of T_3 is negatively directed. From graph to graph after this we notice the T_3 wave becoming gradually more deeply inverted. A turning point, the point of maximum inversion of the T-wave in this lead is arrived at by the thirty-second day. Succeeding records show the degree of negativity receding just as gradually. The T-waves of Lead II throughout followed much the same course as did those of Lead III.

In Lead I after the onset the T-waves became more and more prominent for a time. When their amplitude peak was reached on the fourth day they were large, broad and conspicuous waves with a stilted appearance. After this their amplitude diminished rapidly. On the twenty-first day and again on the thirty-eighth day they were so low as to be practically isoelectric. Latterly they again gradually increased in size. By the sixth month they were once more of fair amplitude and still positive.

The Q_3 wave was significantly deep at the onset. It gradually gained amplitude until, on the eleventh day it was the tallest of any of the deflections of QRS in any lead. Thereafter it gradually declined in size, but even in the last graph remained significantly deep. Q_2 waves were also quite well developed except at the onset. Diminution of voltage of the QRS complexes also affected the amplitude of Q_1 waves, but their relative size from graph to graph seemed to vary in direct proportion with the amplitude of R_1 .

As to alteration of the QRS complexes, their amplitude was quite low at the onset, but voltage dropped still further from graph to graph. After six months, at which time the patient was entirely free of cardiac symptoms and actively going about his business, the amplitude of QRS remained as low, perhaps, as it had been at any time.

CLINICAL-ELECTROCARDIOGRAPHIC CORRELATIONS

How can this seemingly complex series of EKG events be correlated with the probable happenings within the heart of this patient? Why does this series of changes of the R-T levels and of the mutations of QRST com-

plexes seemingly fail to follow the schematic concept of Parkinson and Bedford? Why does the take-off of the R-T serially ascend the R-waves before it changes course to descend and finally reach the isoelectric level? Why do the T-waves change from diphasic to monophasic waves before again changing to the diphasic and then to the completely inverted form? These are some of the questions which occasional electrocardiograms taken haphazard at a few of these phases of transition cannot answer. Their solution can only be attempted on the basis of a serial composed of frequently repeated graphs with clinical detail in sufficient wealth to permit of the formulation of a fairly complete estimate of probable cause and effect.

The probable course of events within the heart of this patient seems quite clear. Thrombosis at the onset probably affected only the terminal portions of the right coronary artery. A-V conduction was not impaired because the blood supply to that node was not inadequate. Beginning on the second day and terminating on the sixth day the violent physical struggles of the patient were almost incessant. This was the cause of the next event—heart block. It was probably brought about as a result of gradual shutting off of the direct blood supply when ascending thrombosis passed the point where the artery supplying the A-V node branches off from the posterior portion of the right coronary artery. This resulted in the appearance in the EKG of first degree heart block. At this point the collateral blood supply to the A-V node derived from the left coronary artery was in all probability quite good. The appearance in turn of a second degree and complete heart block might never have happened were it not for the fact that the violent struggling of the patient brought him to a state of relative insufficiency of the collateral supply. Thus heart block, in all of its phases, was only transitory. As the patient became less violent the collateral blood supply became relatively less and less inadequate. The EKG evidence of this is reversal from complete to second degree block, then from second to first degree block. On the seventh day when the patient, finally completely exhausted as a result of his heavy labors, slept throughout most of the day, all traces of A-V block disappeared—the collateral supply to the A-V node was adequate.

Did the ascending thrombosis go further? If it came around anteriorly almost to the origin of the right coronary artery it would shut off the branch usually supplying the S-A node. This would result in wandering of the pacemaker or sino-auricular block. This did not occur, but the peculiar waxing and waning of the amplitude of the P-waves would seem to suggest that the supply to the pacemaker also, was inadequate. This waxing and waning of amplitude was present only during the period of heart block. The physical exertion of the patient here again probably resulted in relative insufficiency of the blood supply to that node, as the auricular waves promptly became normal after he became quiet. It is not improbable that narrowing of the lumen of the blood vessel supplying the node was already present. Otherwise a state of relative inadequacy of circulation would not have been so readily produced by exertion. The transitory nodal rhythm

and nodal tachycardia that appeared later on were most likely due to the same cause

After the sixth day the patient became quiet and remained so. If we will study the course of the EKG with the viewpoint of a person who has made the first EKG at that point, it will at once be seen that all of those changes which Parkinson and Bedford referred to as a monophasic curve are present. There is perfect R-T fusion. The take-off of T is very high on the descending limb of R in Lead III. There is no suggestion of a downward tip of T₃ pointing below the base line. Following further all of the mutations described by Parkinson and Bedford are in turn manifested until the R-T take-off reaches the isoelectric level, R-T fusion disappears and T is *all* inverted. During this period it is probable that no further ascending thrombosis occurred. Collateral circulation due to the quiet of the patient was adequate for the low level of physical activity present. It was sufficient during the stages of organization of the thrombus and infarct to keep the nodes supplied, to permit of normal conduction through the unaffected portions of the heart, and of eventual clinical recovery of the patient. The reminders that permanent damage had been accomplished were the electrocardiographic residuals—extreme low voltage, deep Q₁, and inversion of T-waves in Leads II and III.

The explanation of the probable course of events within the heart as given above would have seemed fanciful and improbable only a few years ago. At this date there is more than the clinical-electrocardiographic comparison, event by event, to cause this line of reasoning to be more certain than hypothetical. Further on in this paper the background of facts supporting it will be stated.

There is every reason to believe that a quiet patient runs less risk of death from coronary thrombosis than otherwise. The dangers of an ascending thrombosis are feared by every clinician. No matter how they may disagree about whether to give digitalis, glucose, theophylline, caffeine and other drugs, practically all authorities agree that morphine must be given, and in doses large enough to secure relief from pain and quiet on the part of the patient. To this patient morphine was given, and in large enough doses to have caused an average coronary patient to go into coma. But morphine had an antagonistic effect in this case. Instead of promoting quiet and relieving pain, each injection was followed by increased pain and physical activity. When quiet was finally secured it was through the use of sodium amytal. After that the patient went on to an uneventful clinical recovery. The liberal use of injections of caffeine sodio-benzoate and intravenous glucose undoubtedly saved his life during the early days of the thrombosis. Because of potential dangers from the use of the latter it was not given until the patient looked as though he most surely would die. At this point he was cold, pulseless, weak, with deep blue black cyanosis of the lips, dusky gray, almost leaden color of the skin, drenched with perspiration, restless, and with Cheyne-Stokes respiration with long apneic phases.

Notwithstanding the grave condition pictured, the response to glucose was astonishingly prompt. The pain and restlessness were intensified as the patient came back to life, but the shock, cyanosis, and abnormal respiration disappeared, the pulse became palpable, the heart sounds of better quality, the blood pressure increased and he no longer presented the same preagonal appearance. Sodium amytal has been said to lower the blood pressure³⁷ and the use of intravenous glucose in 50 per cent concentration is a dangerous procedure³⁸. It is not our intention here to advocate their use except in carefully selected cases, but rather, by stating how and why they were used in this case, to furnish further material for comparison with the clinical and electrocardiographic events. It may be observed, however, that in a similar T_3 , Q_3 case with complete heart block and Cheyne-Stokes respiration, Bell and Pardee¹⁹ were able to save the life of their patient with the aid of intravenous 50 per cent glucose, and felt that "dextrose intravenously merits trial". Their case also had a stormy course. Other cases of like nature with great restlessness have died.

DISCUSSION

Parkinson and Bedford in 1928 divided their cases of coronary occlusion into T_1 and T_3 groups. They suggested that "the particular coronary branch occluded would determine the lead in which T inversion would occur" and that the T_1 and T_3 types of curve "represent occlusion of different branches". This seemed all the more probable to them in that their case 1 had two separate attacks of coronary thrombosis during a period of two years. The "first attack was followed by the T_1 type of curve and the second by the T_3 type."

Following this up, Barnes and Whitten²⁰ in 1929, after extensive clinical, electrocardiographic and necropsy studies concluded that "an electrocardiogram of the T_1 type is associated with infarction of the anterior portion of the left ventricle supplied by the average left coronary artery" and that "an electrocardiogram of type T_3 was found to be associated with infarction in the posterior portion of the left ventricle in the region usually supplied by the right coronary artery."

Electrocardiograms made in cases of wounds of the human heart,^{21, 22, 23, 24} experimental studies on animals,^{25, 26} and clinical and necropsy findings of other observers²⁷ have confirmed the opinion of Barnes and Whitten insofar as pertains to the electrocardiogram of the average human heart. There are some exceptions of course, but it is probable that they are no more frequent than is variation in the distribution of main coronary branches in exceptional hearts.

Wood and co-workers noted in particular, among other of the principal findings in T_3 cases the presence of a deep Q_3 wave. It is well illustrated in all of their published electrocardiograms of the T_3 type. It should be

observed that Q_1 also was very conspicuous in all of their T_1 electrocardiograms. In a study of electrocardiograms from cases personally observed and from the literature in cases electrocardiographically studied soon after the onset the writer found that either at the onset or some time during the course in T_1 cases (a) both T_2 and T_1 were inverted, (b) 85 per cent had significantly deep Q_3 waves, 63 per cent had well developed Q_2 waves in addition to having significant Q_3 waves. In the absence of R-T, S-T segment deviations the finding of these four changes seems to afford more definite evidence of acute or recent coronary occlusion than does the finding of either of these changes singly.

In the case here reported elevation of the R-T intervals in Leads II and III, inversion of T_2 and T_3 waves, deep Q_2 and significant Q_3 waves are findings all of which are classical and typical of thrombosis of the right coronary artery.

In order to understand the probable effect of ascending thrombosis in the right coronary artery it is necessary to emphasize certain observations concerning the average distribution of that artery. When cardiac infarction occurs as a result of occlusion of the right coronary artery, as pointed out by Parkinson and Bedford and Barnes and Whitten, infarction seldom involves the muscle of the right heart. Even in Barnes and Whitten's Case 12 in which "The right coronary orifice was plugged by a thrombus, all of the right ventricle except a small area adjacent to the septum escaped infarction."

The T_3 type of electrocardiogram is believed by these workers to indicate infarction of the posterior portion of the left ventricle, or more specifically, only that portion of the left ventricle supplied by the terminal divisions of the right coronary artery. The inference is plain that, although the actual infarct is so limited, the occlusion within the right coronary artery may extend even to its orifice. Unless coronary sclerosis is unusually extensive within the vessels supplying the collateral circulation to the right heart it is probable that there is nearly always enough collateral blood supply to nourish it even though its main artery is completely occluded.

Although Barnes and Whitten did not find much evidence of infarction of the right heart in their cases, such infarction has been reported by others, and even aneurysm of the right ventricle has been reported, but such case reports are rare. In the case here reported, and for the reasons given below, it is believed that there was infarction of a portion of the right ventricle.

According to Gross,²⁸ in the average heart the fourth from last main posterior descending branch of the right coronary artery is the *ramus descendens posterior*. In 92 per cent of human hearts he found this vessel giving off the *ramus septi fibrosi* which supplies the A-V node. It was especially noted by him that the *ramus septi fibrosi* receives anastomoses

from the superior septal branches of the left coronary artery. He pointed out that by this means there is available a collateral supply for the A-V node whenever the main source—the *ramus septi fibrosi*—is blocked.

Haas²⁹ cited a case in which such anatomical construction was borne out in a heart where the *ramus septi fibrosi* was blocked by embolism. Hemorrhagic infarction of the muscular divisions which enter into the nodal structure occurred but the *anterior portion of the node was preserved* though much altered by inflammation. Haas explained this preservation of a portion of the node on the basis of collateral supply received from anastomoses with branches of the left coronary artery.

Kugel,^{30, 31, 32} studied 50 normal human hearts and found in all of them a large vessel which he named the *arteria anastomotica auricularis magna*, a branch of the left coronary artery. In 66 per cent of hearts he found that it anastomosed freely with the artery supplying the A-V node. In the remainder he found two main variations, but in each of these the artery was so situated that its anastomoses with the right coronary artery were anterior, and far more proximal to the orifice of that vessel than is the point of branching off of the *ramus descendens posterior*.

Whether from the *arteria anastomotica auricularis magna* of Kugel or from the anastomoses of the *ramus septi fibrosi* with the superior septal branches of the left coronary artery of Gross, it is obvious that the A-V node generally has available a rich collateral blood supply whenever its usual source derived from the right coronary is shut off.

It is probable that only rarely does that node fail to receive a proper blood supply. Acute thrombosis of the right coronary plus extreme sclerotic narrowing of the opposite coronary or of its branches could do this. Occlusion of the right coronary, sclerotic narrowing of the left coronary and temporary insufficiency of blood supply through the left coronary by reason of congestive heart failure or extreme physical exertion could accomplish the same result. In the case here reported it is the most satisfactory explanation of the transient heart block. In a heart already seriously crippled by right coronary thrombosis as here obtained there can be but little doubt that whatever collateral supply was being received through anastomotic branches from a probably sclerosed left coronary artery must surely have been rendered insufficient due to the tremendous struggles of the patient.

As to the sino-auricular node, it is supplied by the *ramus ostii cavi superioris*, a vessel that Gross says "is not absolutely fixed in its origin, for it may arise from either right (60 per cent) or left (40 per cent) coronary artery" and furthermore "there are never two *rami ostii superiores*, always only one."

As before pointed out, occlusion of this vessel might cause wandering of the pacemaker or sino-auricular block. In the case here reported it is probable that the occlusion of the right coronary artery did not extend far enough

anteriorly to occlude the *ramus ostii cavi superioris*. The waxing and waning of amplitude of the P-waves, as noted was more likely due to relative insufficiency of the coronary circulation as a whole due to violent over exertion of the patient. There may also have been present some degree of sclerosis of the proximal artery or of the *ramus ostii cavi superioris*.

The late development of a high take-off of R-T segments has been noted previously by Levine and others. In Levine's case 56 a high take-off developed nearly two months after the onset, but unfortunately no graphs were obtained during the first month after the onset. Thus there was no means of comparing the electrocardiographic status at the two periods. In his case 61 the graph made at the onset does not show a high R-T take-off, but on the second day elevation in Leads I and II is plain, and by the fourth day is marked. Here again the graphs after the fourth day were not made often enough to follow the subsequent course of events, as only three more electrocardiograms were made in the subsequent 26 months. In the case here reported the serial graphs are the first to show both gradual ascent and gradual descent of the R-T segments.

Ball,³³ in a serial of 14 electrocardiograms, was the first to publish a satisfactory serial study of coronary thrombosis with temporary complete heart block. His explanation of the transient nature of A-V dissociation during an attack of coronary thrombosis on the basis of the peculiar anatomy of the blood supply to the A-V node is, with minor exceptions, concurred in by the writer and has been used in part to explain the development of heart block in the case here reported.

The present case study is the twentieth of coronary thrombosis with complete heart block reported in the literature. Ball listed 16 cases derived from the literature and personal communications, overlooking the two cases reported by Wearn³⁴ in 1923. The nineteenth case has been published more recently by Wood and co-workers³⁵. Of the 20 cases, electrocardiograms were made in 18. There were 16 T₁ cases and two T₂ cases. In Sanders'³⁶ case, necropsy showed thrombosis of the right coronary artery with infarction of the greater portion of the outer wall of the right ventricle extending to the apex and to the anterior and posterior portions of the interventricular septum. His case illustrates quite well how even the right ventricle and septum may be extensively involved by infarction in thrombosis of the right coronary artery, though as previously stated, this is exceptional.

SUMMARY

A case of acute coronary thrombosis is reported which is one of exceptional interest for the following reasons

- 1 It is the first case to be reported with serial electrocardiograms at close intervals covering every form of transition of the ventricular complexes from the actual onset of acute coronary occlusion to and beyond the point of clinical recovery. The serial consists of 36 graphs.

2 The gradual mutations of the ventricular complexes can be compared stage by stage with the schematic concept elaborated in 1928 by Parkinson and Bedford. Close clinical-electrocardiographic comparisons are so facilitated by the detail shown in the serial graphs as to enable one to form a reasonable idea of the changes actually taking place within the heart from one phase to another, and to explain how and why they differ in some stages from the succession of changes predicted by Parkinson and Bedford.

3 The case is the twentieth of acute coronary thrombosis with the complication of complete heart block to be reported in the literature.

4 The electrocardiographic changes accompanying probable ascending thrombosis of a coronary artery are serially depicted and correlated with clinical observations.

5 Features of the electrocardiogram tending to make the presence of a significantly deep Q_s wave, in certain instances, more diagnostic of coronary thrombosis are discussed and illustrated by the present case.

Since the preparation of this paper for publication the patient suffered a severe injury resulting in death August 31, 1934. Necropsy, unfortunately, could not be obtained. Prior to sustaining this trauma he had been active physically, with fair tolerance to effort and no complaints referable to his heart. Coronary disease had no connection with his death, nor with the injury responsible for death. Electrocardiograms supplementing those illustrated in this paper were recorded February 28, 1934, March 10, 1934, and August 3, 1934. The first two were essentially the same as the illustrated graph of May 17, 1933. The last EKG, recorded 28 days before death (20 months after the onset of acute coronary thrombosis), showed some changes. QRS had increased noticeably in width and amplitude. R_2 and R_3 were badly slurred. The tallest deflection of any lead (R_1) measured 5 mm. Q_2 and Q_3 measured 1.5 mm and 3 mm respectively. T_2 was very broad and flat, but was slightly positive.

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THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM", A REVIEW OF RECENT AMERICAN AND ENGLISH LITERATURE ON "RHEUMATISM" AND ARTHRITIS *

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IN THREE PARTS

PART II †

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CHRONIC ARTHRITIS

WHEN one uses this term, one is generally speaking of either chronic atrophic or chronic hypertrophic arthritis, the two great forms of "chronic arthritis" which Osgood¹⁸⁷ calls the most generally prevalent and most inadequately treated controllable chronic disease. It is important to use a more specific term than just chronic arthritis and to distinguish between the two forms, as they are probably of quite different etiology, their symptoms and many of their physiologic aberrations are different, their treatment is by no means identical, and above all their prognosis is quite different. These differences have been fully reviewed in the *American Committee's Primer on Rheumatic Diseases and Chronic Arthritis*,¹⁸⁸ to which the reader is referred ‡. The essential differences are briefly these: Chronic atrophic

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† Part I appeared in the *Ann Int Med*, 1935, viii, 1315-1374.

‡ The "Primer" and "Exhibit" can be purchased from the American Medical Association, Chicago, for thirty cents. A statement of British National Medical opinion on chronic arthritis is also available (see reference 383).

(infectious, proliferative, rheumatoid) arthritis may appear at any age but generally does so between the ages of 20 and 40. It involves many joints, small as well as large. If of consequence, it is generally associated with loss of weight and appetite, secondary anemia, atrophy of skin, muscles, and bones, lowered blood pressure and skin temperature, and with other symptoms of vasomotor instability, exhaustion and tachycardia even without fever. Its course may be short and leave little or no significant residual disability. On the other hand it often tends to be progressively destructive, and in uncontrolled cases may end in ankylosis. Its pathologic characteristics in peripheral tissues are fibrous thickening and subcutaneous nodes, and in bone decalcification and infiltration of the epiphysis by nests of small round cells, in articular structures there are synovial proliferation and pannus formation, destruction of cartilage, marginal lipping of bones, and fibrous or bony ankylosis.

Chronic hypertrophic (senescent, degenerative, osteo-) arthritis, on the other hand, rarely appears symptomatically before the age of 40. It tends to involve a few favorite joints, such as the lower cervical and lower lumbar spine, terminal and sometimes middle (rather than the mid- and proximal) phalangeal joints, knees, and less frequently a hip or a shoulder (in the latter situation generally a bursa). Its course may demonstrate little progression, if so, the progression is slow and the disability it produces fairly moderate. It is not associated with a related loss of appetite and weight, anemia, tachycardia, hypotension, or marked alterations in skin temperature, although it is usually associated with some fatigue. Its pathologic characteristics in peripheral tissue are generally none except perhaps minor periarticular thickening, in bone there is no atrophy, in articular structures there are minor synovial fibrosis without pannus formation, cartilage degeneration and sometimes disappearance, early proliferation of marginal and subchondral epiphyseal bone, and no ankylosis except to some degree in the spine as bony spurs may coalesce.

Nomenclature Just as with religion, politics, or prohibition, the subject of the nomenclature and classification of the chronic arthritides arouses vociferous, even acrimonious, debate. No classification of these two joint diseases is satisfactory for all purposes. For various reasons, chiefly to avoid the impression that knowledge on etiology is complete, the American Committee for the Control of Rheumatism has approved the terms "atrophic" and "hypertrophic" arthritis even though as individuals some of the committee members may be in the habit of using other designations. With permissible didacticism one may on occasion wish to use clinical designations (infectious arthritis, senescent arthritis) based on presumed etiology. Under other circumstances one may prefer to use a pathologic terminology proliferative arthritis, degenerative arthritis. Still again a nomenclature in radiologic terms may be preferable.

An etiologic classification based on complete proof may, it is hoped eventually replace all others. In the meantime the others are but working

classifications As long as one realizes the limitations of each term, understanding, for example, that "proliferative arthritis" implies proliferation of synovia not of bone and is therefore the clinical opposite and not the clinical or pathologic equivalent of "hypertrophic" arthritis (which implies proliferation of bone, not synovia), as long as one does not entertain the notion that infection as the cause of "infectious arthritis" is proved with finality, or that all arthritis that shows hypertrophic changes in roentgenograms is "hypertrophic arthritis" in the sense of being the clinical equivalent of senescent arthritis, one should be at liberty to use whatever term seems most appropriate at the moment He who wishes to be completely noncommittal will probably favor the English designation rheumatoid arthritis and osteoarthritis In place of "rheumatoid" or "atrophic" arthritis, the term "infective" arthritis is preferred by Miller¹³³ who believes it is due to streptococcal infection With similar leanings the term "infectious arthritis" is approved for general use by Cecil (1929), Hench (1930), Kauffman,¹⁸⁹ Buie,¹⁹⁰ and many others The term atrophic arthritis is favored by Pemberton,¹⁹¹ Osgood,¹⁸⁷ Matz,¹⁹² Holbrook,¹⁹³ Eaton,¹⁹⁴ Rich,¹⁹⁵ and others Shapiro¹⁹⁶ comments on deficiencies of all classifications and (as did A G T Fischer, 1929) suggests for each form a combined term indicating the clinical, etiologic (wherever possible), pathologic, anatomic, and roentgenologic characteristics of the disease at any particular moment Thus he would speak of subacute, gonorrheal, proliferative monoarthritis, of "hypertrophic arthritis" as chronic degenerative, chondro-osseous, hypertrophic polyarthritis, of "atrophic arthritis" as chronic, streptococcal, proliferative (periarticular atrophic) arthritis For hypertrophic (senescent) arthritis, Miller¹³³ and others favor the term suggested by von Muller, "osteo-arthritis," rather than osteo-arthritis, as the disease is degenerative rather than inflammatory

In congress, physicians should use a common parlance, and in this paper the editors have translated into the Committee's approved terminology the designation used by the author cited Although there may be certain underlying physiologic aberrations held in common by patients with these two great types of arthritis, the majority of workers are more and more convinced that the two types should be considered separately for the reasons noted above, for the sake of prognosis if for no other reason Some still regard them as different expressions of the same disease, among them Knaggs,¹⁰⁷ Willcox,¹⁰⁸ and Clawson and Wetherby¹⁰⁹ Wetherby²⁰⁰ believes that both are forms of streptococcal arthritis, and has grouped both types together in a clinical analysis of 350 cases, in 69 per cent of which patients were women Among points noted were that subcutaneous nodes were present in 31 per cent of 300 cases, and that roentgenograms revealed an "atrophic arthritis" in one joint, such as a shoulder, and a "hypertrophic arthritis" in a knee in the same case (It would appear that part of the author's difficulty in separating types is failure to recognize the difference between the term "hypertrophic arthritis" when used in a radiologic sense,

and the same term when used in the clinical sense Since no attempt was made by him to separate types, his figures cannot be compared with other series analyzed hereafter —Ed)

Roentgenography of Chronic Arthritis In roentgenologic literature there is a tendency to divide arthritis into three groups, following Goldthwaite (1904) atrophic, hypertrophic, and infectious Many have abandoned the third group on the ground that its radiologic characteristics were identical with those of atrophic arthritis The typical roentgenographic alterations of atrophic and hypertrophic arthritis need no review here¹⁹⁸

Scott²⁰¹ distinguishes a third group, dividing hypertrophic arthritis into infectious and noninfectious types Rigler and Wetherby²⁰² studied the roentgenograms of 564 joints of 60 patients with chronic polyarthritis, where pain or deformity was or had been present Twenty-five per cent were radiologically negative, 31 per cent showed changes of atrophic arthritis that is, atrophy of soft tissues and destruction of cartilage and bone, and fibrous ankylosis No case with any degree of new bone formation was held to belong to this group Twenty-three per cent of cases were classed as hypertrophic arthritis with no atrophy of bone, no ankylosis, and little or no cartilaginous destruction Twenty per cent were placed in the so-called "infectious" group, and were characterized by destruction of bone and cartilage and formation of new bone with or without ankylosis While these latter cases appear to be mixed types, they were distinguished from the atrophic group by the presence of new bone formation and from the hypertrophic group by the presence of marked cartilaginous and bony destruction, and also by the character of the new bone formation Hypertrophic changes were not seen in any elbow or shoulder but were largely confined to knees, spinal column, and sacro-iliac region Few atrophic changes were seen in the knees and spinal column The hands, normal in only 5 per cent of cases, showed atrophic arthritis in 45 per cent, hypertrophic arthritis in 9 per cent, and "infectious arthritis" in 41 per cent After the fifth decade of life few joints were normal and hypertrophic changes predominated Of 56 pathologic joints, 37 per cent showed one type, 52 per cent two types, and 11 per cent all three types of involvement Frequently a joint affected more than five years was still roentgenologically negative Noting that "infectious arthritis" appeared more often in those whose illness had lasted longer, or who were older, Rigler and Wetherby concluded that it was but an extreme phase of atrophic arthritis and agreed that the third classification should be abandoned

(It should be noted that the separation was a radiologic and not a clinical one, that weight bearing joints were more prone to show hypertrophic changes, and that although many patients presumably had both types of radiologic arthritis that does not mean that many had both clinical types of arthritis The criteria for "infectious arthritis" used by these authors were not the same as those used by Goldthwaite —Ed)

To determine the presence of adhesions in arthritic joints and the prob-

able value of manipulation Keller⁸⁸ visualizes them by the intra-articular injection of a yellow dye, "arthropsin," a 10 per cent solution of the disodium salt of tetra-iodo-ortho-sulpho-benzoic acid

ATROPHIC ARTHRITIS (INFECTIOUS, PROLIFERATIVE, RHEUMATOID)

Symptoms and Course New series have been analyzed 44 cases by Stecher²⁰³, 48 cases by Rawls, Gruskin and Ressa²⁰⁴, 102 cases by Smith²⁰⁵, 113 cases by Lipkin²⁰⁰, 172 cases by Matz,²¹ and 173 cases by Eaton¹⁹⁴ Analyses have been made of many details, among them sex incidence, hereditary and constitutional factors, presence of allergic phenomena among patients and their families, prodromes, age, various modes of onset and progression of the disease, and related disturbances of endocrine, vascular, gastrointestinal, and locomotor systems In the main, the well-known picture of the disease is again portrayed Here and there a shadow is clarified, a high light toned down, a feature sharpened

The usual sex incidence, 1.5-2 women to 1 man afflicted, prevailed in Smith's and Lipkin's series Matz' patients were all men, war veterans In Smith's series there were 60 women and 42 men, in a former series 325 women and 287 men In 38 per cent of his cases a family history of arthritis was obtained

Factors of occupation played no definite rôle in either Smith's or Matz' series except perhaps in the case of a few minors More patients were of the asthenic than the sthenic or intermediate type, but the disease was not limited to one anthropologic configuration There was no significant correlation between the physical type and the onset of the disease, which seemed to affect brunettes more often than blondes, contrary to expectation Loss of weight may begin early in the prodromal stage At the onset of the disease about 36 per cent of Eaton's patients were underweight, 34 per cent obese During their illness 63 per cent of Eaton's male patients, 48 per cent of his female patients, and 68 per cent of Matz' patients lost weight The average loss of weight was 32 pounds in 18.5 months, with a maximal loss of 100 pounds in six months in one case (Smith) Some patients gained weight even during the course of their illness

Smith stressed the importance of recognizing the prodromes which may be present for a year or more before the onset of symptoms in joints The chief prodromes are fatigue and nervous irritability, but in addition there was a large variety of symptoms referable to the vasomotor, muscular and sensory systems When the disease is established, symptoms in bones are frequently present,—a point not well known Circulatory phenomena are found alterations in pulse rate, blood pressure, color, and in sensation and temperature of extremities, with erythemas, wheals, and other cutaneous manifestations Moderate alterations in blood pressure were noted by all In the majority of Matz' cases the pressure was normal though some patients had moderate hypertension The variations seemed to Eaton to be

as one would expect in any chronic disease, but both he and Smith, who noted evidence of hypertension in some and hypotension in others, remarked that regardless of which alteration was present there seemed to be a definite attempt on the part of the vascular system to maintain an adequate pulse pressure, either through lowering of the diastolic or elevation of the systolic pressure. As the arthritis improves, hypertensive subjects have a lowering of the blood pressure, particularly the diastolic, hypotensive subjects have an elevation of systolic and lowering of diastolic pressures.

The rarity of renal lesions and the relatively frequent secondary anemia were noted, the latter thought to be due to toxemia and poor appetite. While Matz noted no evidence of related allergic diseases, Lipkin and Smith noted it among patients and their families often enough for comment. Lipkin and Matz found no evidence of thyroid or other endocrine disturbance. Forestier²⁰⁷ and Smith²⁰⁵ found the metabolic rate generally to be normal. Smith is inclined to believe that these figures are "false-normals." Recalling that many of these patients had lost much weight, especially in fatty tissue, which has a very low metabolic rate, he considered it possible that where the oxygen consumption at basal levels compared with what it should be for the surface areas based on the weight and height of those patients before their loss of weight, it would be found that the result would be 10 to 20 per cent below normal.

(Many feel that the occasional disturbances of metabolic rate in atrophic or other types of arthritis may result from, rather than be the cause of, the disease. In this connection, thyroid changes noted by Alexandresco and Lautier (1931), in monkeys affected by experimental "infectious rheumatism" after injection of diplostreptococci are of interest. The thyroid changes varied with the intensity, duration, and kind of germ employed. A picture of hyperfunction was produced by attenuated germs after a short infection. With repeated and prolonged infection, a histologic picture of hypofunction resulted. Nodules resembling the Aschoff type were seen—Ed.) Children whose arthritis lasts from 2 to 15 years may, according to Kuhns and Swam,²⁰⁸ develop marked disturbances of growth, the order of frequency being persistence of infantile proportions of hands and feet, asymmetrical development, and dwarfism. While this is favored by non-use and by nutritional and endocrine dysfunction, it is chiefly due to involvement of the proliferating epiphyseal cartilage, resulting in early ossification, and is dependent on the severity and chance location of the arthritis.

Studies on Pathology, Joints. Three monographs serve as the basis of our knowledge of the pathology of articular tissues in atrophic and hypertrophic arthritis: that of Nicholls and Richardson (1909), of Pommer (1913), and of Allison and Ghormley (1931). The last named is to date the most complete study on pathology related to clinical, chemical, and roentgenologic data. Allison and Ghormley (1931) confirmed findings of previous writers, and in addition noted focal collections of lymphocytes in bone marrow and synovia. The last two regions are always attacked

first, and changes in bone and cartilage were secondary to those in marrow and synovia. Brief synopses on pathology of both principal types of arthritis were presented by Eaton.²⁰⁰

All these writers agree on the essential pathologic distinctness of the two types. From an extensive study of the Strangeways collection, Knaggs¹⁹⁷ has concluded that there is no sharp dividing line between atrophic and hypertrophic arthritis. He reported a frequent finding, in cases of atrophic arthritis, of eburnation and extensive marginal lipping, characteristics presumably reserved chiefly for hypertrophic arthritis. On the other hand, ankylosis, not only of the spine but also of carpal and tarsal joints, was frequently exhibited in cases of hypertrophic arthritis. Others have said that, aside from that in the spine, ankylosis does not occur in cases of hypertrophic arthritis. In many specimens features were present on which a diagnosis of either type could be made. Knaggs argues, therefore, that both types "are expressions—at the opposite ends of the same scale—of a single disease," which he believes arises from one toxin, either microbic or otherwise. They are not separate affections but simply names by which two groups of characteristic pathologic changes are distinguished. The two types are, it is true, often distinctive pathologically, but they represent differing reactions, probably to the same insult, which are dependent on "the vitality of the joint tissues and ability to resist or modify the reaction that toxic damage may excite." Knaggs reflects on the fact that patients with hypertrophic arthritis are usually robust and healthy, and that atrophic arthritis is more likely to attack the delicate and feeble. Thus he concludes that "when the tissues are healthy and robust the toxic irritation acts as a stimulus to growth processes and osteo-arthritis results. When the vitality of the tissues is poor, inflammatory reaction may be excited, but in the event that the affected tissues are unable to maintain their vitality in the face of such reaction, degeneration or even disintegration results. In either case, rheumatoid arthritis develops." (This interesting paper would be much more forceful if clinical data had been presented with the pathologic data. The reader could then see how often and to what extent a clinical history of atrophic arthritis was associated with the pathologic findings presumably characteristic of hypertrophic arthritis, and vice versa. Such clinical data, according to Knaggs, are available and should be utilized to strengthen the argument, which otherwise seems somewhat weak if we recall, with Smith,²⁰¹ that atrophic arthritis is confined to no one physical habitus and often appears in the sthenic, robust type—Ed.)

Subcutaneous Nodules—Present in 10 to 25 per cent of cases of rheumatic fever, subcutaneous nodules have been thought to be less common in cases of chronic arthritis. According to Clawson and Wetherby,²¹⁰⁻²¹¹ and Dawson and Boots²¹²⁻²¹³ they occur as frequently, if not more so (20 to 30 per cent), in cases of chronic arthritis, and they are likely, furthermore, to be larger than in rheumatic fever. Dawson and Boots found them only in atrophic arthritis, never in hypertrophic arthritis in spite of diligent

search They believe that their consistent absence in the latter is one more point in favor of the contention that hypertrophic arthritis is an entity distinct from atrophic arthritis Clawson and Wetherby, without separating types, found such nodules in many cases which they think would be called hypertrophic or degenerative arthritis by others Thus they described subcutaneous olecranon nodules in a case in which the patient, a woman 75 years old, had for five years been having pain and stiffness in "toes, ankles, knees, right hip, fingers, wrists and cervical spine," in all areas of which, except the ankles, which were negative, roentgenographic examination showed "hypertrophic arthritis" (It would seem that these authors do not fully appreciate the difference between a clinical and a roentgenologic diagnosis of "hypertrophic arthritis" This patient at 75 undoubtedly had senescent (hypertrophic) arthritis, as everyone at that age has Strangely, however, senescent (hypertrophic) arthritis practically never involves toes or ankles, and the wrists practically never show radiologic change or even clinical symptoms aside from minor pains The patient with that many joints involved undoubtedly had infectious (atrophic) arthritis also, and if the hypertrophic changes were present in all the joints as noted, some of them probably represented the hypertrophic bone reactions of fairly well-advanced infectious (atrophic) arthritis—Ed)

All of these workers agree that the gross and microscopic lesions seen in these nodules are essentially similar to, if not identical with, those of nodules in rheumatic fever, and that they bear no relationship to those seen in yaws, gout, syphilis, or tuberculosis It is further agreed that their common presence in rheumatic fever and atrophic arthritis suggests a close relationship between these two diseases

Laboratory Data Blood Counts, Blood Volume Blood Chemistry The nonfilament count was found by Steinbrocker and Hartung²¹⁴ to be elevated in 100 per cent of 50 cases of atrophic arthritis It was normal in 52 per cent and elevated in 48 per cent of 50 cases of hypertrophic arthritis When it was elevated in cases of hypertrophic arthritis, the average elevation was less (22.3 per cent) than in cases of atrophic arthritis (31.5 per cent) When the count is normal (nonfilament count 15 per cent or less), the patient in all likelihood does not have atrophic arthritis When it is elevated he may have either type if it is markedly elevated in all probability his arthritis is of the atrophic type

In 250 undifferentiated cases of "chronic arthritis" Eaton²¹⁵ found only three with normal blood counts Characteristics were slight secondary anemia, normal or slightly low leukocyte counts, a tendency toward lymphocytosis, eosinophilia in 10 per cent of the cases (highest eosinophile count 9 per cent) and the appearance of juvenile cells causing in 90 per cent of cases a nuclear shift to the left in a Schilling hemogram To Cecil^{216, 217} the presence of immature polymorphonuclear cells suggested infection above all else

The blood volume of 26 patients with atrophic arthritis whose average

weight was normal was found by Sparks and Haden²¹⁸ to be 12 per cent above the normal average, the increase being due entirely to an increase in plasma. Since it is assumed that in spite of this the joints are receiving a poor blood supply, it may be deduced that the excess volume is held in splanchnic vessels. If so, the beneficial effect of breathing and postural exercises is explainable.

A review of the literature on the chemistry of the blood in both types of arthritis is presented by Eaton and Cocheu²¹⁹ in addition to studies in 304 cases in which 183 were of the atrophic and 121 of the hypertrophic type. In both types the values for blood sugar, urea, and creatinin, were essentially normal. There was a tendency toward a moderate increase in blood uric acid,—in a number of each type there were values between 4 and 5 mg. Values more than 5 mg. per 100 c.c. were found in only two cases of atrophic and in four of hypertrophic arthritis. No significant changes in serum calcium or serum phosphorus or in calcium and phosphorus metabolism were discovered by Bauer, Bennett, and Short²²⁰ either in cases of atrophic or of hypertrophic arthritis.

The phosphatase test was found by Race²²¹ to be normal in 10 cases of atrophic and in 11 of hypertrophic arthritis, and it was also normal in nine cases of fibrositis and in two of gout. It is likely to be slightly elevated in spondylitis of the ankylopoietic type, and it is generally abnormal in types of osteitis, often reaching values five to ten times that in the arthritides. Race concluded that the phosphatase content is normal in diseases in which joint structures only are significantly involved.

Many (e.g. Cecil²¹⁷) have noted that the sedimentation of erythrocytes is more rapid in atrophic than in hypertrophic arthritis. In atrophic arthritis it is usually above 30 mm. in one hour (Dawson and Boots²¹⁸, Rawls, Gruskin and Ressa²⁰⁴) and parallels to an extraordinary degree the severity and extent of the arthritic process. In hypertrophic arthritis the rate is usually normal (less than 10 to 15 mm. in one hour), although it is occasionally 20 to 30 mm. it is rarely above that value. Thus the test will help to differentiate the two forms. The rate is also elevated, however, in gonorrheal, gouty, and tuberculous arthritis, it is normal in fibrositis and neuritis.

The average figure for the sedimentation rate at the end of one hour in atrophic arthritis is 42 mm., according to Forestier²⁰⁷, in 16 per cent of cases it is between 10 and 20 mm., in 20 to 30 per cent between 20 and 30 mm., in 30 per cent between 30 and 50 mm., in 26 per cent between 50 and 80 mm., and in 5 per cent between 80 and 120 mm. While the sedimentation rate generally varies with the clinical course of atrophic arthritis and decreases as the patient improves, in some cases it remains elevated in spite of clinical improvement, according to Oppel, Myers and Keefer⁶². Single estimations are of little value, but repeated observations may give information of prognostic significance.

Kling²²² has developed a method for the comparative estimation of the

sedimentation rate of blood corpuscles in synovial fluid and plasma by replacing the plasma with equal volumes of fluid. The severity of infection in a joint is better illustrated by the sedimentation of corpuscles in synovial fluid than in the blood, the rate in the latter reflecting the general bodily reaction rather than the articular reaction. Thus in a case of monoarthritis, if the rate in synovial fluid is low but that of the blood is high, some other infection than that in the joint should be considered responsible for the rapid sedimentation rate. A more accurate differentiation can be made between atrophic and hypertrophic arthritis if one has the opportunity of studying the sedimentation rate and viscosity of synovial fluid. Noninflammatory fluids with a low protein content have a low comparative sedimentation index and a low viscosity. Fluids with a high content of mucin show a low comparative sedimentation index but a high viscosity.

Electrocardiograms Master and Jaffe²¹⁷ found only the slightest evidence of myocardial involvement by means of electrocardiographic examination of 17 patients with atrophic arthritis. In acute rheumatic fever, abnormalities were found consistently. A normal electrocardiogram would thus speak for the former in attempting a laboratory differentiation between acute or subacute atrophic arthritis and rheumatic fever.

Etiology and Pathogenesis of Atrophic Arthritis An appreciation of differing views on the etiology of rheumatic fever will partially suffice to explain those regarding atrophic arthritis, since the same general diversity of ideas also relates to the latter. Theories on the cause of atrophic arthritis can be grouped under four headings: (1) infectious, (2) metabolic, (3) endocrine, and (4) neurogenic. The same variants of the infectious theory are held as for rheumatic fever. In atrophic arthritis the other theories, especially the metabolic, have more support than in rheumatic fever. The speculative literature in this field is voluminous and is not subject to review here. Several comprehensive considerations have appeared recently (Eaton¹⁹⁴, Cecil²¹⁷, Bauer, Bennett and Sholt²²⁰, Pemberton,²²³ Os-good,¹⁹ 187 Dawson and Boots²¹³, Clawson and Wetherby,¹⁹⁹ Miller¹³³ Burbank,²²⁴ Key³⁶).

The Infectious Theory This theory has three chief variants: the bacterial, the protozoal, and the virus. Some (e.g. Kendall, 1931) would add a fourth variant,—causation of the disease by a mutation form, which is not merely a mutable streptococcus but an organism that may become a virus on suitable mediums. The latter variant has been sharply challenged and has not received confirmation.

Bacterial Variant The bacterial variant has the same three subvariants which were discussed under rheumatic fever: (1) the bacteremic idea of direct infection from focus, through blood to affected tissues, (2) the idea of bacterial toxemia and (3) the idea of bacterial allergy. Essentially the same type of schema (table 4) can be erected for atrophic arthritis as was displayed for rheumatic fever (table 2). In many of the brackets the same names can be appended, sometimes with minor variations,—a different strep-

TABLE IV

Bacterial Variants of the Infectious Theory of Atrophic Arthritis

(The names are representative only)

I *Bacteremic variant*

(a) Group specific one type of organism held responsible

- 1 *Staphylococcus* Crowe (1927) *Staphylococcus albus*, "micrococcus deformans"
- 2 *Streptococcus hemolyticus* Gray, Fendrick, Gowen (1932)
Cecil, Nicholls, Stainsby (1929)
- 3 *Streptococcus viridans* Clawson, Wetherby (1932)
- 4 *Streptococcus*, indifferent

(b) Not group-specific more than one type considered potentially responsible

- Streptococcus viridans* (generally) Rosenow (1914)
Staphylococcus more often than *streptococcus* Key (1929)
Streptococci, diphtheroids Ashworth (1932)
 Strauss (1932)
Streptococcus hemolyticus and *viridans* Hadjopoulos and Burbank (1932)
 Pleomorphic Cadham (1932)

II *Toxic variant*

(a) Group (and strain) specific

- Streptococcus cardio-arthritis* Small (1927)

III *Allergic variant*(a) *Group specific*

- 1 *Streptococcus hemolyticus* Dawson, Olmstead, Boots (1931)
- 2 Other organisms

tococcus, perhaps, being incriminated. Similar bacterial and immunologic investigations provide the basis of the arguments (table 5). Many who were able to obtain striking results in blood and tissue cultures and agglutination tests in rheumatic fever also obtained unusual results in atrophic arthritis, but the data are about as inconclusive, as open to varied interpretation, and as subject to critical debate as those in the case of rheumatic fever.

The reasons for the various conclusions are obvious. If an investigator finds bacteria in a significant number of foci and the same type of germ frequently in blood and affected tissues, the chain of circumstance seems complete in favor of the bacteremic theory. If blood cultures are repeatedly negative, yet the patient presents certain immunologic reactions that seem to be peculiar to an infectious disease (the property of agglutinating one or more organisms in high titer, hyperactive skin reactions, and so on), and if the observer further considers the pathologic changes in affected tissue to be consistent with an infection, it seems reasonable to conclude that infection is the cause but that it operates either through its toxins or bacterial antigens to which tissues are hypersensitive. When so many different germs are isolated from blood and when skin reactions and agglutination tests are not uniform, the germs under consideration must either be considered unrelated invaders or one is forced to favor the allergic hypothesis. To date no one variant is proved.

Blood Cultures. Reviews of the bacteriology of blood in atrophic arthritis have been made by several, among them Cecil²¹⁶ (Bernhardt and Hench (1931) found that up to 1932, at the hands of all workers and by

TABLE V
INFECTIONOUS THEORY OF ATROPHIC ARTHRITIS
Basis of approval of bacterial subvariants
(The names are but representative)

| Test | | Result |
|-------------------------------------|--|--|
| Culture of blood | (a) <i>Characteristic</i> | (1) Group specific attenuated hemolytic streptococci—Cecil, Nicholls, and Stainsby (1929), Gray, Fendrick and Gowen (1932) Plcomorphic form (bacillary and diplococcal)—Traut (1933) |
| | (b) <i>Not characteristic</i> | (2) Not group specific various streptococci and diphtheroids—Ashworth (1932), Strauss (1932) (Generally negative) Burbank and Hadjopoulos (1927), Kracke and Teasley (1932), Nye and Wavelbaum (1930), Margolis and Dorsey (1930), Bernhardt and Hench (1931), Dawson and Boots (1932), Ashworth (1932), Lichtman and Gross (1932) |
| Culture of joint tissues | (a) <i>Characteristic</i> | (1) Group specific attenuated hemolytic streptococci—Cecil, Nicholls, and Stainsby (1929), Gray, Fendrick and Gowen (1932)—“alpha prime” |
| | (b) <i>Not characteristic</i> | (2) Not group specific <i>Streptococcus viridans</i> and indifferent—Rosenow (1914) <i>Streptococcus viridans</i> and (or) <i>hemolyticus</i> —Billings, Coleman and Hibbs (1922), staphylococci and streptococci—Key (1929) (Or generally negative)—Forkner, Shands, Poston (1928), Margolis and Dorsey (1930) Nye and Wavelbaum (1930), Dawson, Olmstead, Boots (1932) |
| Agglutination | (a) <i>Characteristic</i> | (1) Group (but not strain) specific <i>Streptococcus hemolyticus</i> —Cecil, Nicholls, Stainsby (1931), (attenuated <i>Streptococcus hemolyticus</i> —Dawson, Olmstead, Boots (1932), Gray, Fendrick, and Gowen (1932) Ashworth (1932), Myers, Keefer, Oppel (1933) |
| | (b) <i>Not entirely characteristic</i> | (2) Not group specific staphylococci and streptococci—Crowe (1924) <i>Streptococcus viridans</i> and <i>hemolyticus</i> —Clawson and Wetherby (1932) Agglutinins also possessed by controls, but in lower titer |
| Skin sensitivity | (a) <i>Characteristic</i> | (1) Group specific <i>Streptococcus viridans</i> —Clawson, Wetherby (1932) |
| | (b) <i>Not entirely characteristic</i> | (2) Not group specific <i>Streptococcus viridans</i> and <i>hemolyticus</i> —Birkhaug (1929), Lautman (1932) Pilot (1932), Myers, Keefer, Oppel (1933) |
| Complement fixation (streptococcal) | (a) <i>Characteristic</i> | Hastings (1913) Burbank and Hadjopoulos (1925) Crowe (1925), Munro (1925) |

| | | |
|---------------------------------------|--|---|
| Culture of lymph nodes | <i>Generally positive</i> | <i>Streptococcus viridans</i> —Rosenow (1914) Forkner, Shands, Poston (1928) Pleomorphic (bacillus-diphtheroid-coccoid)— Cadham (1932) |
| Culture of subcutaneous fibrous nodes | <i>Generally positive</i> | <i>Streptococcus viridans</i> (diplococcus)—Clawson and Wetherby (1932) |
| Culture of stools | <div> <div> <i>Generally positive and characteristic</i> <i>Negative</i> </div> <div> Crowe (1927), Burbank (1932), Vaughan (1932) Dawson and Boots (1932) </div> </div> | |
| Experimental arthritis | <i>Generally positive to suspected organisms</i> | Rosenow (1914), Cecil, Nicholls, Stainsby (1931) Hadjopoulos and Burbank (1932) Cadham (1932) |

different methods, a total of about 780 cases had been studied. In 74 per cent blood cultures were sterile. Various organisms were isolated in 26 per cent. Streptococci of various types (generally *viridans*) were isolated in only 18 per cent. Organisms other than streptococci were found in the remaining 8 per cent. The percentage of positive cultures obtained by different workers varied tremendously, from 69 per cent to none, the highest being that of Cecil, Nicholls, and Stainsby (1929). —Ed)

Several recent additional studies are reviewed. By a modification of Cecil's method, Gray, Fendrick and Gowen^{107, 108} isolated streptococci "from the blood or joint fluid or both" in 61 per cent of 144 cases. The organisms were of the alpha (*viridans*) or alpha prime type in 95 per cent of the cases, and of the gamma (hemolytic) type in 5 per cent. Those isolated in atrophic arthritis were only very slightly different from those found by them in 71 per cent of 28 cases of rheumatic fever.

Ashworth²²⁵ and Straus²²⁶ found various organisms in the blood in 41 per cent of 138 cases. In 28 per cent of 39 cases an organism resembling the "typical strain" (attenuated hemolytic streptococci) of Cecil, Nicholls and Stainsby was found. In 13 cases a diplococcus was found. There was considerable pleomorphism noted in subcultures, many streptococci being at first considered diphtheroids. Straus believed both the diphtheroids and the streptococci to be of etiologic importance, and he favored the multiple streptococcal (and multiple bacterial) theory as against a single etiologic species. A pleomorphic type of organism was isolated by Traut²²⁷ from the blood in 71 per cent of 38 cases. It was primarily a bacillary or diplococcal form, although some were coccoid forms in chains. Clawson's technic was used. Traut emphasized the fact that to obtain positive blood cultures successfully, prolonged cultivation and the recognition of the likelihood and importance of pleomorphism and dissociation is necessary. (Animal experiments are not mentioned in these four reports and no evidence is given that the organisms isolated were atthrotropic. —Ed)

No significant organisms could be found by Haden,²⁻⁸ by Dawson, Olmstead, and Boots,²⁻⁹ who made 105 blood cultures in 80 cases using the method of Cecil, Nicholls, and Stainsby, or by Lichtman and Gross,²³⁰ who

studied 48 cases. Different organisms were isolated in a small percentage of cases, but they were similar in type and frequency to those from controls. The study by Lichtman and Gross of 5,233 consecutive blood cultures in a general hospital showed that, with adequately sensitive methods, an incidence of nonhemolytic streptococcemia (alpha and gamma types) between 4 and 15.5 per cent (average 6 + per cent) occurs in at least nine different diseases, and that on the basis of the incidence of the transient bacteremia alone, these organisms cannot be considered of etiologic significance.

Agglutination Tests These tests have given more uniform results, and it may be significant to note that whereas in the past *Streptococcus viridans* has been considered the most likely offender, suspicion is now being cast more on hemolytic streptococci. The findings of Cecil, Nicholls and Stainsby (1931) have apparently been confirmed by several groups of workers. Although Dawson, Olmstead, and Boots recovered no significant organisms from blood, they²³¹ found that the serums of the majority of patients with atrophic arthritis possessed the property of agglutinating several strains of hemolytic streptococci to an extraordinarily high titer. Tests with a number of other organisms revealed little or no agglutination except to R pneumococci, which were agglutinated to almost as high a titer as the hemolytic streptococci.

Agglutination tests to hemolytic streptococci were positive in 74 to 80 per cent of the cases of atrophic, but in no case of hypertrophic arthritis seen by Gray, Fendrick, and Gowen. Ashworth, using Cecil's strain, noted positive results in 89 per cent of 65 cases of atrophic, but in none of 100 cases of hypertrophic, arthritis. Keefer, Myers and Oppel¹¹⁰ using four strains of hemolytic streptococci, found that 55 per cent of 22 patients with atrophic arthritis and 15 per cent of 28 patients with hypertrophic arthritis had positive serum agglutinins. There was no evidence of strain specificity, nor were they correlated with an unusual sedimentation rate or positive skin reactions to nucleoprotein of hemolytic streptococci. They and Dawson, Olmstead and Boots agreed that the reactions differ from the type which, as Tillett and Abernethy¹⁴¹ showed, occurs in certain febrile human serums. It is also agreed that reactions do not become significantly positive for several weeks after the onset of the disease, and that they depend, in part, on the severity of the arthritis. Dawson, Olmstead, and Boots felt that their presence is related to the duration of the disease and the age of the patient, an idea to which Nicholls and Stainsby^{231a} could not agree. Haden²²⁸ was unable to find agglutinins to *Streptococcus viridans*, and, although those to hemolytic streptococci were frequently obtained, they were also found in a high percentage of control cases. He therefore doubted their significance.

The significance of these reactions is but little understood²³². They are thought to suggest, but not to prove, some etiologic relationship between arthritis and the organisms involved. As the disease recedes, titers generally fall and tests become negative. Clawson and Wetherby believed that they rise higher in patients to whom streptococcal vaccine is given intravenously.

than in those treated subcutaneously, and are an evidence of developing immunity Fletcher²³³ however, insists that a rise in blood agglutinins does not always indicate favorable change Whatever their significance agglutination tests will apparently differentiate atrophic and hypertrophic arthritis

Cutaneous Tests Intradermal tests were performed by Clawson and Wetherby,^{200, 210, 211} using a green streptococcus More arthritic patients (types not separated) gave positive reactions thereto than did controls, but the reactions in a given case were of little significance Anderson²³⁴ and Pilot²³⁵ were unable to get consistent reactions with dilute toxins of hemolytic or other streptococci Lautman²³⁶ considers such reactions of some diagnostic significance Others, while admitting that they apparently indicate a hypersensitivity of the particular person to the organisms used, believe the evidence that there is some relationship between the disease and the organisms that produce the skin reaction is by no means conclusive (Clawson and Wetherby¹³⁹, Myers, Keefer and Oppel²³⁷) It has been claimed that in certain allergic diseases, a substance, probably a proteose, can be isolated from the patient's urine which, when injected intradermally, gives a skin reaction similar to the reaction of antigen in an allergic patient sensitized to that antigen It has also been stated that a flare-up of joint manifestations can be brought out thereby in certain cases of atrophic arthritis Aldred-Brown and Munro²³⁸ prepared autogenous urinary vaccines in 50 cases In all cases skin tests were negative to scratch and patch tests Six patients were treated with weekly injections of proteose, five were not relieved

Cultures of Joint Tissues Streptococci were frequently isolated from joint fluid by Gray, Fendrick, and Gowen, as noted No significant organisms were found by Dawson, Olmstead, and Boots in aerobic and anaerobic cultures of 23 specimens of synovial fluid

Cultures of Lymph Nodes, Fibrous Nodules, and Stools From 27 of 34 regional lymph nodes, Cadham²³⁹ isolated a diphtheroid with pleomorphic characteristics Primary cultures, which took 14 to 21 days to develop, were sometimes a coccoid type resembling minute streptococci, with bacillary forms in subcultures Arthritis was experimentally produced in rabbits He believed they were probably identical with organisms originally isolated by Schuller (1892), from nodes by Rosenow (1914), and occasionally from blood by Burbank (1925)

A diplococcus or *Streptococcus viridans* was isolated from subcutaneous fibrous nodules cultured by Clawson and Wetherby No attempts to produce experimental arthritis are recorded Although Dawson, Olmstead and Boots²²⁹ recovered no organisms from such nodes on culture, their appearance was that of an inflammatory granuloma, and their structure was highly suggestive of an infectious process

The isolation of presumably significant organisms in feces has been further reported on by Vaughan,²⁴⁰ Meader,²⁴¹ Burbank,²⁴² and Traut²⁴²

Allergic Diseases and Arthritis To lend support to the theory of bacterial allergy, inquiries have been made regarding the coexistence of arthritis with diseases thought to be allergic. Such diseases were found by Aldred-Brown and Munro in only two of 50 patients with atrophic arthritis and in only one of their families. Harkavy and Hebard²⁴³ noted among 400 patients with asthma only nine with arthritis. Elimination of atropens to which they were clinically sensitive relieved neither the asthma nor the arthritis. The treatment of sinus and ethmoid infections was followed by complete subsidence of the arthritis in eight of the nine cases, with some relief of the asthma also. Rackemann²⁴⁴ rarely found a history of "rheumatism" in patients with asthma and hay fever.

Allergic Theory and Experimental Arthritis (Synovitis) Several have produced arthritic changes by sensitizing animals to bacterial or nonbacterial proteins and then injecting the antigen into joints. Similar results have been obtained if the antigen was injected into joints, later into the blood. Brunschwig and Henry²⁴⁵ questioned whether these changes were allergic or due to other factors. Their experiments indicated that while acute and chronic inflammatory changes in synovia and adjacent tissues can be produced by products of bacterial decomposition and metabolism (filtrates of various bacteria), almost identical reactions are produced by such foreign proteins as egg white and human blood serum. They consider them the result of a direct action of foreign proteins on synovia rather than an allergic phenomenon. The early eosinophilia noted does not necessarily indicate allergy but may be accounted for by the soluble nature of the noxious agents used, since eosinophiles are cells of defense against soluble toxins.

Comment on the Infectious Theory Only a few of the workers who have attached etiologic significance to certain organisms have determined their arthrotropic potentialities to the extent of trying to produce experimental arthritis in animals. Of the more recent workers, Cecil and his colleagues, and Hadjopoulos and Burbank²⁴⁶ produced subacute and chronic arthritis with clinical and pathologic features considered identical to those of atrophic arthritis. The organisms injected were recovered from the blood and many of the tissues of the affected animals. Such experiments have been vital to the idea of a bacteremia and direct bacterial infection, but they are laborious and expensive. Nevertheless, it is unscientific to attribute pathologic properties to an organism, and useless to make an "autogenous vaccine" therefrom just because it happens to be located in an arthritic patient's stool, throat, or other "focus." Much of the strength of the streptococcal theory has been vitiated by arguments over the cultural differences in organisms isolated. Much of the worth of vaccine therapy has been discounted because "autogenous vaccines" have failed to help, vaccines made from organisms utterly unrelated to the patient's disease.

Bacteriologists are too much concerned with differences in cultural reactions and not enough with determining the pathologic propensities of the streptococci isolated—their tropism or peculiar infecting power. The re-

quirements of some, that all streptococci isolated must have identical cultural reactions to be of significance, is fallacious, according to Rosenow²⁴⁷ who has shown by a long series of experiments that streptococci isolated in cases of chronic arthritis, irrespective of whether they were green producing, indifferent, or slightly hemolytic, possess peculiar localizing and disease producing powers. Of such organisms, arthritropism was exhibited in 53 per cent of 1,447 animals injected therewith, with invasion of other tissues in much smaller (1 to 8 per cent) numbers.

The estimation of the electrophoretic potential of different organisms presents a new and simple method for determining their pathogenic properties without the difficulties of other and older methods. Bacteria, in the presence of an electric field, act as ions and carry a negative charge. Cultures of suspected foci are inoculated into warmed glucose brain-broth and incubated overnight. The top two c.c. of the culture are poured off into a scrupulously clean test tube and centrifuged for 10 minutes. The sedimented bacteria are suspended in 12 c.c. of distilled water. This suspension is then poured into an electrophoresis apparatus, of the Northrup-Kunitz-Mudd type, and under standard voltage and other standard conditions the rate of 20 or more streptococci is determined by noting, with a stopwatch, the number of seconds required for the germs to travel a unit distance of 32 microns. The higher the charge, the faster is the rate of travel toward the positive pole. Streptococci, which repeated animal experiments show to be arthrotropic, have their own rate of migration. Neurotropic organisms have a different speed of migration. The velocity of normal saprophytes and of many types of organisms has been established, that of arthrotropic organisms, for example, is chiefly 2.22 microns per second per volt per centimeter. The blood serum in cases of atrophic arthritis has a slowing effect on the rate of migration, far greater than the serums of encephalitic or poliomyelitic patients have in slowing "neurotropic" organisms. Adsorption experiments with arthrotropic streptococci removed specifically from the serum of patients with arthritis this power of reducing velocity. These investigations, Rosenow feels, explain much regarding the mutability of streptococci and the conception of elective localization. It is much more important to study and to try to alter a germ's habits regarding disease production than its habits of color production on mediums. The latter can be changed without always changing the former, and vice versa. Using this method, which is of great diagnostic help, it is no longer necessary to inject cultures from a focus of infection intravenously into animals and to make cultures from their joints in order to be certain that the streptococcus isolated may be etiologic. According to Rosenow the determination of the cataphoretic velocity will usually suffice.

Other Theories on the Cause of Atrophic Arthritis There have been no important additions to the data on which the parasitic or virus variant of the infectious theory was based. (In regard to the idea advanced by Ely,²⁴⁸ Barron²⁴⁹ and others, that arthritis might be related to an ameba, it may be

significant to recall that arthritis is not so far a reported complication or aftermath of the Chicago epidemic of amebiasis in 1933 —Ed) New evidence in support of the endocrine, metabolic, and neurogenic theories will be discussed together, since proponents who formerly were inclined to incriminate one system, such as the endocrine, now generally believe that an interrelated disturbance may be responsible for arthritis. Thus they speak of disturbances of the "endocrine-sympathetic system and the chemical and metabolic alterations associated therewith." Those who do not accept the primary importance of bacteria in the production of atrophic arthritis generally believe that the predisposing factor is an inherent physiologic weakness. The precipitating factor may or may not be an infection, but the main factor is some as yet undiscovered metabolic disturbance, some alimentary toxemia, more likely to be chemical than microbic.

There are several variants to each of these theories of the endocrine, that it is a disturbance of thyroid metabolism, of the parathyroid, suprarenals, ovaries, or other endocrine glands, alone or in combination. Variants of the metabolic or chemical theory are that the disease is due to (1) a perversion of food chemistry, (2) food allergy, (3) vitamin deficiency. Disturbances in the utilization of carbohydrates, of calcium, magnesium, or phosphates, and of sulphur have all been suspected. Eaton¹⁹⁴ has reviewed current data on these ideas.

It is generally agreed that the soil in an arthritic patient is probably peculiarly altered to permit the later development of the disease. The tendency to asthenia, inadequate circulation, and poor thermo-regulation are signs of an inherent weakness or "rheumatic diathesis," which Llewellyn^{158 159} and Jones^{161 162 200} have long thought to be due to hypothyroidism. They believe that the storage in skin of amino acids, tyrosine, and cystine may be of fundamental and etiologic importance. Tyrosine is the mother substance of which the thermo-regulating hormones, thyroxine and epinephrine, are chemical derivatives, and also of melanin. Tyrosine enters into the formation of insulin, another heat-producing hormone, and the sulphur content of insulin is derived from cystine. These writers suggest that ultra-violet rays may be of value in arthritis because they increase the tyrosine, and hence potentially the thyroxine and epinephrine in blood.

Thyroid Dysfunction and Arthritis The appellations "endocrine rheumatism" or "menopause arthritis" refer generally to the hypertrophic form, but disturbances of thyroid or ovarian function are held by some to be an important, if not the main, cause of atrophic arthritis also. Continuing his earlier study (1928) on the relationship of thyroid disease to chronic arthritis, Duncan²⁵¹ reported cases in which severe joint pain lessened markedly following thyroidectomy for hyperthyroidism. Either form of preexisting arthritis may be aggravated by a metabolic variation in thyroid function above or below the normal level, but especially by hyperthyroidism. Especially can relief be given by thyroidectomy in cases in which articular pain has appeared during the course of the hyperthyroidism. Such cases

Duncan is inclined to group separately,—joint pains being due neither to "atrophic" nor "hypertrophic arthritis" but to hyperthyroidism itself. In such cases pain was referred to one or both shoulders, with involvement of the hands, particularly on the side on which the shoulder was implicated. Generally, the pains were not relieved by usual measures, including bed rest, but marked relief was frequently experienced within a few hours after thyroidectomy. (Since the joints continued to improve, one infers that the relief was not of the temporary nonspecific type that an arthritic patient may experience after almost any surgical experience—Ed.) Hypothyroidism is more likely to be associated with slowly progressive, degenerative articular changes. They are in part relieved by thyroid administration.

Four patients with advanced atrophic arthritis and with elevated metabolic rates (+ 18 and + 16, + 60, + 25, + 35) were seen by Lautman²⁵². The appearance of the first patient was so suggestive of hypothyroidism rather than hyperthyroidism that small doses ($\frac{3}{4}$ grain) of thyroid extract were given for 10 days, after which the metabolic rate had fallen to — 10 per cent, rather than increased. On the basis of this experience, thyroid extract was given to the other three patients also. In each case the paradoxical reaction of a lowering of the rate was noted. (The author speculates on the reasons therefor. In only one of these cases was the initial metabolic rate checked. One wonders whether the rates given were really basal, and whether the thyroid preparation was active or absorbed. The presentation of such a paradoxical reaction, noted after repeated estimations of the rate, to extracts of proved potency or to injected thyroxine would be of considerable interest—Ed.)

Pemberton²⁵³ early noted that the metabolic rate of many arthritic patients is lowered, not because of difficulty in combustive processes alone but from a condition of vasoconstriction in finer vessels, especially in muscles, which induces a relative anoxemia or anemia resulting in dysfunction of tissues in which the combustive processes are initiated. In 36 per cent of 106 cases of atrophic arthritis Hall and Munroe²⁵⁴ found rates below — 10 per cent. In 18 per cent of cases it was below — 17 per cent. The lowered rates were thought to be due to enforced inactivity. Signs and symptoms of hypothyroidism were seen less frequently than in hypertrophic arthritis. They concluded that thyroid deficiency was not so important a factor in atrophic as it may be in hypertrophic arthritis, but that, when present, its correction may be helpful in a small (17 per cent) number of cases. The basal metabolic rates were normal for all but eight of 65 patients with "chronic arthritis" seen by Martin²⁵⁵. In the eight cases the rate was below — 20 per cent.

Alterations in Nutrition and Blood Chemistry The opinion of those who favor the metabolic theory is that bacteria play only a minor (perhaps precipitating or complicating) rôle, and sometimes none at all, in the production of atrophic arthritis, and that some metabolic error, arising from a disturbed alimentation and circulation, is the causal factor in producing

the disease among persons who have inherited or acquired the proper soil therefor. Pemberton believes that 50 per cent of all patients inherit a background characterized by an asthenic body build, instability of the nervous and vasomotor system, and lack of intestinal tone. It is on such a soil that arthritis becomes engrafted as the direct result of some as yet unidentified toxic agent. Such a chain of events is manifested by many obvious chemical and physiologic aberrations, some of which can be corrected with benefit to the patient. The chief proponents of this theory are Pemberton, and his colleagues, and Osgood, in the United States, and Fletcher,²⁵⁶ in Canada. Their writings are too well known to need review here.²⁵⁷ Fletcher, and Pemberton and Peirce²⁵⁸ again note the frequency with which arthritis of both types is accompanied by enlargement and tortuosity of the large bowel. Sometimes the condition is congenital, sometimes acquired. Once established, it may be an aggravating factor in some cases of arthritis, an original exciting factor in others. They believe that the use of a diet low in carbohydrates and calories, and high in vitamins especially vitamin B, may be followed by a complete or partial restitution of the intestinal abnormality and by considerable cessation of arthritis. Such treatment must be applied, however, only in appropriate cases, and only on the basis of familiarity with the principles concerned. (While Fletcher and others have produced atonic bowels in rats which were given inadequate amounts of vitamin B, so far no definite arthritis has been produced in any experimental studies with foods or vitamins in deficient or excessive quantities—Ed.)

Considering that the cecum is the source of absorption of most of the bodily fluids, Barrow²⁴⁹ feels it is highly probable that toxins responsible for arthritis are elaborated therein and absorbed therefrom. Such toxins may be of several sources: from dissolution of body cells, bacterial endotoxins and exotoxins, abnormal food chemicals, and possibly also toxins either elaborated by, or resulting from, lysis of protozoa, the presence of which he feels is more than coincidental.

The changes in the colons of 25 patients with "chronic arthritis" (undifferentiated) and 25 controls ("average dispensary group") were studied by Haft.²⁵⁹ Incompetency of the ileocecal valve was found in 80 per cent of the arthritic patients, and in 16 per cent of the controls, lack of haustration in 64 per cent and 78 per cent, atony in 40 per cent and 8 per cent, and redundancy in 85 per cent and 80 per cent, respectively. Thus Haft concluded that these intestinal changes were not typical of arthritis but could be found in any chronic disability associated with malnutrition and inadequate diet. Any one of these variations may occur without symptoms. They may be the result, not the cause, of disease, but their correction may be helpful. Repeated fluoroscopic examinations of the colons of 65 patients with "chronic arthritis" demonstrated to Martin²⁵⁵ no variation which he viewed as abnormal, considering the patient's build, age, and abdominal muscle tone. Minor changes were frequently found by Holbrook,¹⁹³ major alterations rarely.

In considering the etiologic importance of intestinal disturbances one must distinguish between the bowel as a focus of infection and as a source of intoxication from abnormal food products. The latter may depend in part on the former, but it is the second idea that the adherents of the metabolic theory stress, believing that arthritic patients either eat foods which are poisonous to them because of idiosyncrasy, or partition their food unhealthily in the direction of an excess of one type of food, such as sweets and starches. Eaton^{260, 261} surveyed the eating habits of 270 patients with atrophic arthritis, but found no discernible differences between their habits and those of nonarthritic persons. Their diets contained adequate amounts of protein, vitamins, calcium, and minerals, and there was no evidence of an imbalance in favor of either acid or alkali-forming foods. Alcohol or tobacco seemed to be of no significance. (Detailed food charts are given, but they were not summarized as to the relative amounts and type of carbohydrates used—Ed.)

Noting a "tendency" to increased values of uric acid in blood and synovial fluid of patients with chronic arthritis, a "feeble attempt" on the part of such patients to adopt a low purine diet, and reports to the effect that uric acid metabolism may be related to allergy, Eaton considers "chronic arthritis" and allergic disease related to an unknown precipitating factor, excess uric acid serving as the predisposing factor. (The uric acid values recorded—the method was not stated—are by no means consistently high and one would agree with the author that the data are insufficient for final conclusions.) Martin also noted somewhat high values of blood uric acid in a number of cases of "chronic arthritis."

Abnormal sugar tolerance curves were noted in a high percentage of the cases by Martin and by Shackle and Copeman,²⁶² although fasting levels of blood sugar were essentially normal, as was also shown by Eaton and Cocheu.²¹⁹ The sugar content of both arterial and venous blood was determined by Shackle and Copeman. Had the difference between these two levels been less than the normal differences, they would have agreed with Pemberton that the cause of the rapid rise of the blood sugar in atrophic arthritis might be due to a failure of muscles and other tissues to utilize sugar, thus causing "unused sugar" to increase the amount in returning venous blood. In the majority of cases, however, normal or even greater differences were observed, similar to those seen not infrequently in true diabetes. In spite of clinical improvement, there was no marked improvement in subsequent tolerance curves.

Studies on Circulation and Skin Temperature Opinions regarding the frequency and significance of circulatory alterations in arthritis are conflicting. It has been stated that patients with atrophic arthritis generally have a lowered skin temperature of the extremities, low blood pressure, and a reduction in size and number of surface (nail-bed) capillaries. It is assumed that a similar state of affairs occurs in joints, and that this is a potent factor in initiating and keeping up the disease. Kovacs, Wright,

and Duryee²⁶³ studied 40 cases of atrophic arthritis and 40 of hypertrophic arthritis. A subnormal surface temperature was found in an equal number of the cases (in 52.5 and 50 per cent, respectively). A decrease in the number of capillaries was seen in 30 per cent of the cases of atrophic arthritis but not in cases of hypertrophic arthritis except in fingers with pronounced Heberden's nodes. Small constricted capillaries were seen in 53 per cent of the former, 28 per cent of the latter, a slow blood flow was present in 65 and 52 per cent and tortuosity in 35 and 60 per cent of these cases, respectively. There was a definite relationship between slow blood flow, lowered surface temperature, and increased sedimentation rate. However, none of the circulatory changes consistently paralleled the activity or extension of the arthritis, and because the changes were not consistently present they could not be considered of etiologic importance. Furthermore, it is not established that the condition of nail-fold capillaries is duplicated by articular capillaries. The skin of arthritics is slightly less responsive to histamine tests than normal skin, according to Bisset and Woodmansey²⁶⁴ who also noted paucity of capillary loops but considerable attenuation, with long straight loops readily visible. Patients with atrophic arthritis show a lag in the return of color and temperature to extremities after the application of the Moskowitz test (the alternate application and removal of a tourniquet). Rich¹⁹⁵ believes this affords evidence of a diminished circulation. According to Bick,²⁶⁵ patients with atrophic arthritis display hypotension and a frequent tendency toward a progressive narrowing of the dorsalis pedis artery, or at least a diminution of its pulse. Atrophy and discoloration of skin are early evidence of insufficient circulation which generally remains compensated. However, in the Montefiore Hospital, there are always several cases of end-stage rheumatoid arthritis in which vascular obliteration is so far advanced that one or even several extremities have become gangrenous as a result of vascular obliteration and an added neurotrophic factor. Biopsy of articular tissue and bone in cases of old inactive atrophic arthritis showed hypovascularity, with a decrease in size and number of smaller vessels and extensive atrophy of bone, probably due to decrease in vascular patency. (The editors recall but one somewhat similar case—a case of Osgood's in which there was extensive trophic changes of skin and nails but no definite gangrene. Since related gangrene in atrophic arthritis has not been reported, a finding that could hardly escape attention, one wonders whether unrelated vascular occlusion may not have been present in Bick's cases. More studies are desirable, particularly on the frequency and time of appearance of such circulatory changes in normal persons and chronic invalids of different ages. So far, no control studies have been presented by anyone. Not a few arthritic patients with severe but afebrile arthritis have warm, not cold, hands, as Drukker and van Breemen²⁶⁶ have shown. Of 100 patients, 16 and 22 had always had cold hands and cold feet, respectively. Thirteen patients noted cold skin with the onset of their

arthritic pains Twenty-four had blue hands after the disease started, but 23 still had warm hands and 10 had warm feet—Ed)

TREATMENT OF ATROPHIC ARTHRITIS

A program of treatment based on an acceptance of the infectious theory naturally differs in principle and in some particulars from one based on an adherence to the metabolic or endocrine theory At the hands of thoughtful specialists, however, these differences are by no means as great as one might suppose, because the deficiencies of each theory are only too well recognized by them and the inadequacy of a program narrowed to fit some favored hypotheses is sometimes too painfully apparent In one case the initial emphasis may be laid on removal of infected foci and on an attempt at bacterial immunization or desensitization In another, first consideration may be given to the insurance of proper nutrition and intestinal elimination In the last analysis, however, the considered therapeutic program of the majority of those of wide experience in the care of arthritis is essentially the same, not as different as one might infer from the publications of each where a favorite theme is, with entire propriety, emphasized The skeptic or therapeutic nihilist may suggest that, faced with a progressive and resistant disease, the "infectious theorist," for example, will soon enough come to the end of his road and gladly try the schemes of another It is not for this reason, however, that physicians are adopting a broader viewpoint and an inclusive plan of treatment, but because modern studies have shown how intricate is the disease called atrophic arthritis, and how imperative it is to approach it by every possible avenue The statement is not borrowed without justification "Know arthritis and one knows medicine" Testifying to the profession's enlarged outlook is the increasing recognition of the importance of studying the soil of the affected patient and not just the seeds of disease, of recognizing phenomena which subtly but often unmistakably announce the prologue to rheumatism These prodromes have been reviewed unaccustomed fatigue and chilliness, transient pains in muscles and joints, vague vasomotor and sensory disturbances, mild declines in appetite and weight (Painter,²⁶⁷ M Smith,²⁶⁸ Minot²⁶⁸) It is often difficult to appraise such complaints In the beginning one must certainly treat them with discretion and not be a prophet of impending doom Once they are unmistakably and significantly present, a reasoned plan of attack is in order, first things first Readily removable foci of infection should be cared for promptly Gentle regulation of the daily habits of the patient is apropos—the establishment of a daily budget of rest and moderate nontraumatizing activity, of a balanced diet, and proper elimination Painter rightfully insists that when adequate treatment is instituted in the prodromal and early stages of rheumatism, much permanent joint injury can be prevented, often the disease stops forthwith Unfortunately no statistics are available concerning the thousands of persons with whom

arthritis has but flirted, to be driven away by gracious Nature, aided perhaps by an alert general practitioner. Were such data revealed, it would surely give encouragement and a more proper perspective to those who see the other thousands who procrastinated or were neglected until the disease was firmly established. No program of treatment is suitable for these patients en bloc. Treatment must be individualized to fit the person perhaps more than his disease. It will be conservative or radical as circumstances of the moment dictate. In appropriate cases, it may be altered frequently, or remain essentially unchanged for weeks. With this foreword, a review of current methods and opinions of their worth are given.

Recognition and Management of Infected Foci Ryerson²⁶⁹ considers infected *tonsils* the commonest cause of atrophic arthritis. Foci "above the vocal cords" are probably primary, according to Burbank²⁷⁴, those below the cords are secondary. An unusual infection was considered by Fitzgibbon²⁷⁰ to be a probable focus, for example, the esophagitis of a woman, aged 31, who developed a progressive polyarthritis after "pneumonia." Shortly thereafter, she had "pulmonary tuberculosis." Still suffering with arthritis in spite of removal of infected foci, she noted difficulty in swallowing. Dilatation for cardiospasm was followed, curiously, by "striking improvement" in both her general and joint condition. Three years later arthritis and cardiospasm recurred simultaneously. After another esophageal dilatation both cleared up. While pregnant, a year later, the cardiospasm but not the arthritis recurred. Shortly after pregnancy was completed, both the arthritis and cardiospasm again recurred and were once more relieved by esophageal dilatation.

A recent study of *sinus infection* in relation to arthritis has been made by Snyder, Fineman and Traeger,²⁷¹ and Hurd,^{272 273} who believe that sinusitis is as common and as important in arthritis as is tonsillitis. Many cases of "silent sinusitis" are missed. Sixty-eight per cent of 386 consecutive patients with atrophic or hypertrophic arthritis had "pathologic changes" in the sinuses, 74 per cent of the latter showed infection both clinically and roentgenologically and 17 per cent of them gave no history suggestive thereof. Fifty-four per cent of 43 patients whose sinusitis was untreated failed to show improvement in joints. Seventy-one per cent of 28 patients whose sinuses were treated conservatively and 89 per cent of 18 whose sinuses were operated on were "cured or showed marked improvement." Roentgenograms, transillumination, direct examination, and douching are all considered necessary to reveal the "silent" cases, some of which may be purulent.

A spray of an appropriate bacterial emulsion is recommended by Burbank for the "local vaccination" of chronic nasopharyngitis.

Although the *gall-bladder* is not a common focus, it is infected in about 3 to 5 per cent of cases of atrophic arthritis, according to Judd and Hench.²⁷⁴ In some cases cholecystitis and infections of joints bear an indirect relationship, both probably arising from some other and primary focus. In other

cases, infections of the gall-bladder may serve as a focus for arthritis, as it may harbor organisms, generally streptococci, but occasionally staphylococci or bacilli, capable of producing experimental lesions in the joints and gall-bladders of animals. Bacteriologic and pathologic observations have been made in 55 cases of chronic infectious arthritis in which cholecystectomy for coexistent diseases of the gall-bladder was performed. In several cases, gall-bladder tissue contained arthrotropic organisms. In five cases symptoms related to joints were completely relieved, in eleven cases there was marked improvement, and in eight there was definite, although moderate, relief following operation, a total of 52 per cent. The joints of the remaining 21 patients were not appreciably affected by cholecystectomy. Judd and Hench concluded that when definite surgical indications for cholecystectomy are present, it is justifiable to urge surgical intervention in the hope that the arthritis may be definitely benefited. Further experience is necessary before one can urge removal of the gall-bladder for arthritis when the indications for operation, aside from the arthritis, are not definite. A conservative attitude is probably desirable, yet the nature of chronic infectious arthritis is so malicious that a radical attitude in individual instances may be justified provided surgery is advocated and accepted without unwarranted promise of benefit.

According to Hartung and Stembrocker²⁷⁶ the incidence of gall-bladder disease in chronic arthritis is 4.5 per cent (nine of 200 consecutive cases of arthritis, three cases with infectious arthritis and six with osteo-arthritis). This was an incidence no higher than that in any general hospital's admissions. Of the 200 arthritic patients, 30 were suspected of having cholecystitis or stones by history or physical examination, but in 25 cases cholecystograms were negative. By microscopic and bacteriologic examination of the material obtained by duodenal drainage, four of these radiographically normal gall-bladders were found to be affected. On the basis of these statistics, and from the fact that no relief to joints was provided by cholecystectomy and duodenal drainage in one case, it was concluded that cholecystitis is apparently not an etiologic factor. (The tropism of organisms isolated by drainage or at operation was not determined by the latter workers. The failure of treatment in one case is insufficient to permit conclusions on the results of otherwise indicated cholecystectomy in arthritis.—Ed.)

The possibility of the *bowel* being a focus for arthritis remains a vexing question. This problem is aside from that concerning the likelihood of its containing food toxins. Space forbids that we discuss auto-intoxication in extenso here. Many believe that arthritis originates from intestinal bacteria (Smith²⁷⁶ and Traut²⁴²). Traut and Herold²⁷⁷ found streptococci (viridans and hemolytic) more commonly on the rectal mucosa of arthritic patients than on those of controls, but the number found bears no relationship to the severity of the disease. Fifty-three of 60 arthritic patients showed such germs (but only three of 15 controls). The patients'

serums contained strong agglutinins thereto. Exacerbations and remissions of joints were related to variations in "gastrointestinal dysfunction". The germs, when injected intravenously into rabbits, did not produce arthritis but did so occasionally when injected into the colon.

Infections of the genito-urinary tract (prostatitis and vesiculitis) were the only foci found by Hayes²⁷⁸ in 40 per cent of 50 cases of arthritis. In many more such infection was found in association with infected teeth or tonsils. When conservative treatment fails to afford relief in the face of progressive arthritis, radical measures, even vesiculectomy, may be justified. When *endocervicitis* is present, pelvic diathermy and ionization may be helpful (Robinson²⁷⁹).

Time for Removal of Foci. The optimal time for, and the dangers incident to, removal of foci have long been the concern of many. "Cruel as arthritis is, few of its victims lose their senses." That that is left for their physician to do is the inference one gains on reading the critique of one (Mayers²⁸⁰) who, while granting a meed of praise to focal removal, insists that patients have been made temporarily worse or even permanently crippled by the removal of infected teeth at the wrong time. Gruesome "before and after" pictures are shown: one of a young man "before removal of a tooth" and "two days later—permanently blind", one of a boy "before alveolectomy" and the same patient later "dying of endocarditis which appeared four days after removal of a tooth", three others who suffered "rapid destruction of eyes after tooth extractions". The appearance of such reactions may be prompt or delayed. "The fuse the dentist has lighted is a long one and the explosion may not take place for a week, a month or even several months." Adequate preparation and technic will tend to minimize or prevent such catastrophes.

(The editors lay claim to not a little experience in the field of focal removal for arthritis but confess that significant exacerbations after removal of foci, long heard of and much looked for, have very rarely, and in the case of most of us never, materialized. Reports such as these generally give no statistics on the number of removals followed by no reaction, or on the normal expectancy of minor and major flare-ups in the course of arthritis without focal removal. Until such data are at hand, based on our own experience, we feel that the bugaboo of a significant postoperative flare-up is considerably overemphasized. That some, without painting so dire a picture as the one above, do not entirely agree with us is however evident from the following—Ed.) "The early removal of foci is indicated but the patient should be built up before undertaking debilitating surgical procedures" (Minot²⁸³). "In the beginning it is more important to destroy the infection than to remove foci. Extraction of teeth may admit streptococci into the blood stream. After the infection has disappeared either spontaneously or as a result of treatment consideration of possible foci may then be investigated" (Miller²⁸¹). "Focal removal should be performed only when the patient's general condition has been improved with

the aid of autogenous vaccines" (Anderson²³⁴) "Foci in some cases should at first be left alone, to be dealt with after the general condition has been greatly improved" (Crowe²⁸²) "In some of the more febrile cases a real hazard exists in removal of foci, which are not removed during or near an acute phase of the disease, and before the removal of which a transfusion is occasionally given" (Holbrook¹⁹³) (In the face of a progressive arthritis, when the "building up processes" do not otherwise materialize, procrastination in removal of foci certainly seems unwarranted, and the risk thereof is justified if foci are removed in conformity with good clinical and surgical judgment—Ed.)

The removal of foci in patients whose arthritis is many months or years ("five years or more", Holbrook¹⁹³) old is rarely if ever followed by improvement in joints. Their removal early may be of great value. The effects were noted by Miltner and Kulowski²⁸³ in 100 cases of atrophic arthritis. Of 37 patients less than 16 years of age, 73 per cent were "apparently cured" and 16 per cent "markedly improved." Of 63 patients more than 16 years of age, only 15 per cent were "cured," but 58 per cent were markedly improved. Of 100 patients with hypertrophic arthritis, none were cured and 91 per cent received no improvement from removal of foci. According to Stansby and Nicholls,²⁸⁴ removal of foci is more likely to help than vaccines. Fifty-eight per cent of 103 patients with atrophic arthritis were "improved" after tonsillectomy. Sixty-nine per cent of 35 patients were improved after the removal of abscessed teeth. Vaccines helped only 36 per cent. Complete and permanent cure following removal of foci was exceedingly rare, but a rather high percentage were "favorably affected." Some foci probably responsible for arthritis are permitted to remain because criteria for the estimation of infection therein are often too rigid.

Others are disappointed by removal of foci. In Holbrook's cases of nonfebrile atrophic arthritis, no one patient was unquestionably benefited thereby. In his other group ("atrophic arthritis with evidences of infection," fever, malaise, red or hot joints), early removal of foci many times abruptly halted the disease.

Dietotherapy Diets are given in arthritis to reduce or to eliminate a supposed auto-intoxication (food), to reduce a presumably etiologic intestinal infection, to correct a supposed deficiency in minerals or vitamins, to remove the irritating trauma of obesity or to increase the patient's "non-specific resistance" (Hench²⁸⁵). It is obvious that there is no one "diet for arthritis", it depends more on the patient than the disease for which diet is given (Minot²⁸⁶).

Since most of his patients had digestive disturbances (intolerance to starch), Traut²²⁷ reduced the starch content of their diets with reported improvement. Pemberton's diet (low in carbohydrate, low in calories) is approved by Bethea,²⁸⁷ and by Meader²⁴¹ who sees no warrant for withholding meat or "acid" fruits unless a definite idiosyncrasy is proved. Pemberton's diet was associated with no significant improvement in the

cases of Wetherby,²⁰⁰ and of Seybold.²⁸⁸ Fletcher's diet, in which emphasis is placed on vitamins (with a low carbohydrate intake advised chiefly to enhance the utilization of vitamins), was approved by Buckley²⁸⁰ and by Holbrook.¹⁹³ According to Brown,²⁰⁰ the food factor in arthritis has been overestimated, and many patients suffer from over-dieting. Physicians, misled by false analogies to gout, too often restrict meats, an adequate supply of which is vital to combat anemia, fatigue, and loss of weight. Restriction of proteins often does more harm than good, according to Fletcher,²⁰⁰ who finds no chemical support for the use of alkaline diets and is rarely able to demonstrate definite food idiosyncrasy or allergy.

The use of small doses of *insulin* (generally with a high-calorie diet) is recommended as a "fillip" for weak, anemic, underweight arthritic patients with anorexia or loss of appetite by Shackle and Copeman,²⁶² Ellman,²⁹¹ Eaton,²⁶¹ and Fletcher.²⁰⁰ Ellman uses five units daily for one week, injections being given 20 minutes before the principal meal and followed by glucose or milk to avoid hypoglycemia. The insulin is increased weekly by five units until 30 units (15 units, twice daily) are given. When all other measures fail, appetites can thus be stimulated. Eaton used 5 to 30 units (twice daily) in conjunction with a high-caloric diet.

Additional Intestinal Therapy Supposed intestinal antiseptics are still being recommended: acidophilus milk (Smith²⁷⁰), colonic irrigations (Miltner and Kulowski,²⁸³ Ellman,²⁹¹ Burbank²²⁴), mineral oil, and mild cathartics or preferably oil retention enemas (Holbrook). Burbank treats the gastrointestinal tract by the use of a bland, low carbohydrate diet and daily capsules of saponified heart tissue lipin. Ryerson²⁹⁰ utilizes a two week "laxative test" as an indication for intestinal therapy, but he fails to say what should be done thereafter if joint pains are reduced. At times Smith relieves ileocecal stasis surgically.

Vaccines Come depression or prosperity it's a poor season indeed that doesn't present its "vaccine of the year" for atrophic arthritis. Since the popularity of each lasts a span of years, at any given time there are several "favorites" extant. Some of them in current favor are those of Burbank, Cecil, Clawson and Wetherby, Crowe, Rosenow and Small. In addition numerous physicians "go on their own" to make and use personal vaccines from autogenous strains.

Cecil favors a three to four months' trial of vaccine, using his typical strain. All symptomatic reactions are avoided. Better results were obtained for private than for dispensary patients, and by the intravenous rather than the subcutaneous route. His colleagues, Stainsby and Nicholls,²⁸⁴ obtained "improvement" in 36 per cent of 194 patients treated with vaccine alone. The results were essentially similar regardless of the type of vaccine (autogenous or stock) used and regardless of the method of administration (subcutaneous or intravenous).

On the basis of animal experiments in which agglutinins were augmented by the intravenous more than by the subcutaneous route, and from

which evidence was obtained suggesting that subcutaneous vaccines tend to increase rather than to decrease the hypersensitive state, Clawson and Wetherby^{199, -200} treated 365 patients with "chronic arthritis" (undifferentiated) by the intravenous route, using their favorite "rheumatic fever strain" Eighty per cent had clinical improvement manifested, in most cases after 10 injections in five weeks Improvement as a rule did not occur until the agglutinating titer of the patient's blood rose to 1 6400 or more, and foci of infection were not removed until such a concentration of agglutinins had been obtained thereby

Autogenous and complement-fixing strains, mainly of streptococci, are used by Burbank²²⁴ in doses small enough to avoid reactions The complementary titer of the patient's blood is, he believes, an index to the value of vaccine Burbank's vaccine or autogenous vaccines, prepared after the method of Burbank, are used by Anderson,²³⁴ by McBride²⁰² and by Ryerson²⁶⁹ with "marked improvement in many cases" Patients with both atrophic and hypertrophic arthritis were treated by Burbank and Ryerson Some of them, especially those with hypertrophic arthritis, were not benefited in any way So far as Ryerson could see these vaccines harmed no one Burbank's method of preparing vaccines includes killing the organism by phenol rather than by heat, a method which Hoover feels makes them more specific Hoover²⁹³ obtained "good results" with a large majority of those willing to accept "a rather long period of treatment" (no statistics given) Most of these workers rely on measures other than vaccine alone

Crowe believes that atrophic arthritis is primarily due to *Staphylococcus albus*, with streptococci as important but secondary invaders, that hypertrophic arthritis is due primarily to streptococci, secondarily to *Staphylococcus albus* (This makes vaccine therapy convenient indeed) Eight hundred and two patients have been treated with weekly injections of Crowe's stock vaccines alone Crowe and Young,²⁹⁴ in their second report (first report Lancet, 1930), analyzed results in 65 cases of atrophic arthritis, 245 of hypertrophic arthritis, 218 of "mixed types," 217 of fibrositis, 38 of neuritis, and 21 of "other types" Results in the atrophic, mixed, and hypertrophic group, respectively, were symptom free 17, 6, and 8 per cent, much improved, 35, 40, and 32 per cent, improved, 32, 42, and 46 per cent, and not benefited, 16, 12, and 14 per cent "Striking improvement" generally occurs between the tenth and fifteenth week of treatment The size of doses depends on the patient's reactions In one case the same dose (the smallest dose that gives relief without reaction) may be used for months A fifth of the patients tend to have a relapse in spite of continued treatment More than 40 per cent go on to further improvement (The authors admit that no controls were available While results were based in part on examinations, they were apparently graded largely by the patients' answers—Ed)

Crowe's vaccine alone was used by Thomson²⁹⁷ in the treatment in 106 cases 25 atrophic, 44 hypertrophic, 12 "mixed," and 25 fibrositis Re-

sults are not analyzed for separate groups. Of the patients, 25 per cent were "completely relieved" of symptoms, 65 per cent were considerably relieved, and 10 per cent had little or no relief. (These results are after one to 10 months of treatment, a time entirely too short for a thorough appraisal. *No controls are given—Ed.)

Autogenous vaccines, made from various strains of streptococci from different sources (blood, synovia, feces, foci, lymph nodes) and given by different routes and in differing doses (initial dose from 15 or 20 (Rawls, Gruskin and Ressa²⁰¹) germs to 100,000 germs) are preferred by many (Goldfain,²⁰⁶ Cadham,²³⁹ Lautman,²³¹ Ashworth,²²⁷ Gray, Fendrick, and Gowen,^{107, 108} Vaughan,²¹⁰ Traut,²¹² Miller,²⁹⁷ Meader,²⁴¹ Buckley²⁸⁴). In some instances only those strains were used to which the patient was skin-sensitive. Small doses were favored with the idea that desensitization, not immunization was being accomplished. In 48 cases 81 per cent of patients were improved by intravenous vaccines of various streptococci isolated from throat cultures by Rawls, Gruskin, and Ressa²⁰⁴. Specificity was presumed if agglutinative titers were greater than 1:160. Cadham noted "some amelioration" in 80 per cent and "complete relief" in many, of 90 cases of "chronic polyarthritis" in which he used autogenous strains presumably of the peculiar pleomorphic organisms isolated by him from regional lymph nodes. Vaccines made from germs isolated from feces were used by Vaughan (47 per cent of 100 patients with "chronic arthritis" improved satisfactorily) and by Traut²¹². Forty-eight per cent of 27 patients with "chronic arthritis" treated by Traut without vaccine recovered or were greatly relieved. Thirty-one patients unrelieved by other measures were treated by vaccine. 68 per cent were markedly or completely relieved. Agglutinins to these strains were present in high titer in patients' serums before therapy was instituted.

Speaking of "fecal vaccines" for arthritis, Brown²⁹⁰ says, "I never subscribed to the view that if you couldn't find a septic focus anywhere you could at least give vaccines prepared from intestinal flora. I always felt that it was a poor bowel that couldn't give something."

In contradiction to the adherents of vaccine therapy, many are "disappointed" in vaccines, and use them skeptically or not at all. According to Miller¹³³ "their value is still open to question." Minot regards them as "of doubtful value," possibly harmful if reactions are produced. To Ellman²⁰¹ they are "unsatisfactory." Kinsella's²⁹⁸ experience with streptococcal vaccines and extracts was "not encouraging."

Congdon²⁰⁹ treated 331 patients with "infective arthritis" either with autogenous or stock vaccines, the latter prepared from 40 strains of *Streptococcus viridans* isolated from infected foci. A smaller number of controls were observed. Congdon concluded that such vaccines do not hold out any better prospect of improvement or cure than other current methods.

Of 103 patients treated by Stainsby and Nicholls,²⁸⁴ 20 had tonsillectomy alone, 83 had tonsillectomy and streptococcal vaccine intravenously or sub-

cutaneously Improvement was no greater for the latter than for the former An estimation of the value of vaccine must consider its psychological effect and the fact that some patients will improve any way

In the treatment in 100 cases Holbrook¹⁹³ used almost every combination of antigen and method of administration for nearly every degree of atrophic arthritis Repeated skin and agglutination tests and clinical criteria were used in evaluating results He concluded "undoubted clinical improvement, not easily accounted for otherwise, occurred only occasionally No single one of the above groups did well enough to show clearly superiority of results over other groups not receiving vaccine Our best results with vaccines have occurred where an autogenous organism which showed a strong positive skin sensitivity test, was used in small desensitizing doses intravenously We have had a few dramatic results in this group of patients" Dawson and Boots²¹³ treated several hundred patients with atrophic arthritis, using small and large doses of autogenous vaccines subcutaneously and streptococcal "antigens," typhoid vaccine, and hemolytic streptococcal vaccine subcutaneously and intravenously As controls, some were given weekly injections of minute amounts of isotonic sodium citrate They concluded that their value remains unproved It was found impossible to influence favorably the sedimentation rate in general Those treated otherwise than with vaccines were equally improved

Pemberton²⁵³ regards vaccines as a definite arm of medical therapy "However, (he says) in many arthritic clinics vaccines are rarely required In Philadelphia we have to hunt to find cases in which they are really needed I have difficulty in getting such cases to show to postgraduate students"

To appraise the value of vaccines, Miller²⁸¹ obtained the opinions of a number of internists, immunologists and bacteriologists His conclusions were as follows (1) The not infrequent, brilliant therapeutic results which seem clinically to follow vaccine administration justify the belief that vaccines do have a rôle in the comprehensive treatment of the arthritic patient The specific indications for the use of vaccines, their optimal dosage or method of administration, etc., are still open questions At the moment it would appear that vaccine therapy in chronic arthritis is appropriately limited to the atrophic form, and has little, if any, application in the hypertrophic type (2) The consensus of opinion inclines to the view that the mechanism whereby improvement occurs under vaccine administration is in some way related to a desensitization process rather than to the formation of specific antibodies In harmony with such a conception, small doses of vaccine are most advocated, given preferably intravenously, and continued over a long period of time, avoiding pronounced constitutional reactions (3) Regardless of whether this conception is substantiated or not, it would seem apparent that in the light of more recent bacteriologic studies, greater attention should be paid to the process of vaccine preparation, chiefly in terms of attempting to secure virulent strains of the autogenous disease-provoking organisms and the avoidance of such measures as promote antigenic dissociation in

preparing the vaccine for therapeutic use (4) At present there are no so-called immunologic or laboratory procedures which are established standards or indexes of the therapeutic value of vaccines in the comprehensive program necessary for any arthritic patient Finally, it is to be hoped that more rigorous regard for some of these principles which have been briefly alluded to, will, for the time being, both retard the extravagant claims which are made by some as to the value of vaccines in chronic arthritis, and at the same time provoke a more serious consideration of the definite purpose for which vaccines are used

(As do others, the editors of this review differ on the value of vaccines Two favor their use, two use them only occasionally, two do not use them at all All are agreed however that a trial of vaccine therapy is entirely justified for a patient whose painful arthritis is "standing still" or getting progressively worse, uncontrolled by measures used In such cases reactions should be avoided, the patient should not be promised too much but be told that it may or may not help, and the cost of vaccine administration should be light, under no circumstances should it be a burden—Ed)

Antistreptococcal serum seems to be rarely used Goering³⁰⁰ reported beneficial results in one case

Foreign Protein Therapy Similar differences of opinion exist as to the value of foreign protein therapy It has the approval of Miller,¹³³ Dill,³⁰¹ Goering³⁰⁰ and Hench³⁰² Murray-Lyon³⁰³ treated 28 patients with foreign proteins intravenously, 16 with peptone, 12 with typhoid vaccine They all showed a greater immediate response to treatment than did 12 control patients but at the end of one to five years the results for the two groups were very similar Meader²⁴¹ and Ryerson²⁶⁹ noted temporary improvement only, and Meader feels that the danger of serious exacerbation and of irreparable injury is too great to warrant its use

To determine the type and incidence of such dangers Hench³⁰² reviewed his experience with the administration of about 10,000 injections of typhoid vaccine intravenously to 1,500 patients with atrophic arthritis and to 1,000 with other diseases He also made a complete survey of the literature in search for reports of unusual and untoward reactions The reactions were in general well-borne, and Hench concluded that the beneficial results from protein therapy justify its continued use and further development Unusual reactions to such treatment have been rare at The Mayo Clinic, they occurred in 14 cases in all, an incidence of about 0.5 per cent They occurred 16 times in the treatment of 11 patients with atrophic arthritis, once in a case of rheumatic fever and three times in the treatment of two patients with occlusive vascular disease Thus, of 10,000 injections, only 20 were followed by an unusual reaction, an incidence of 0.2 per cent

The mechanism of both the usual and unusual reactions is fully discussed Unusual reactions result from the stimulation of inflammatory foci of either infectious or noninfectious origin, stimulation of latent diathetic phenomena, and from some marked vasomotor or intravascular

chemical change that may produce acute thrombosis or vasomotor imbalance. Thus the unusual reactions occurring subsequent to injection were acute and subacute appendicitis, cholecystitis, enteritis, pleurisy, pericarditis, iritis, glaucoma, adenitis, vascular thrombosis, and renal insufficiency. Death occurred in three instances, a mortality of 0.12 per cent (about 1 in 1,000 patients). This constitutes a very small risk but a risk that must be recognized and that can probably be avoided by more careful selection of patients, using it with special caution for patients over 50 years of age and not at all for patients markedly exhausted or debilitated. Except in certain conditions, of which pulmonary tuberculosis is one, the known presence of latent or quiescent foci should not act as a contraindication to foreign protein therapy. Indeed, part of the value of such treatment lies in the possible demonstration of suspected or unsuspected foci otherwise undemonstrable at the time. Such reactions, if their significance is appreciated, may be advantageous rather than detrimental. The recognition that such reactions may very occasionally occur, will lead to a more judicious use of such treatment, but the compilation of reported reactions should not give them undue emphasis to the detriment of a useful and essentially safe form of treatment.

Transfusions A series of small blood transfusions has been advocated by Copeman³⁰⁴. Holbrook treated 70 patients in this manner and found that in the subacute and early phases of "infectious arthritis" with or without anemia, they responded well and in not a few instances dramatically. The temperature may drop to normal, the pulse be slowed, joint effusions disappear, and the patient gradually recover. Transfusions were of little help for chronic afebrile patients with advanced bony changes. Transfusions of 300 c.c. of blood weekly, for debilitated patients, are advocated by Bure¹⁹⁰.

Various Medicinal Preparations The debatable value of various anti-rheumatics has been recently reviewed, Hanzlik (1929), Young (1930), and Mutch (1931). Bethea²⁸⁷ cites the use of 88 "anti-rheumatic" drugs, ascribing worth to only a few. Dill³⁰¹ and Kauffman⁷⁰⁵ describe the rectal administration of salicylates to patients who have a systemic aversion to their oral use. Ascending doses of 50 to 250 grains of sodium salicylate are given, twice a day, by rectal injection or drip with four to six ounces of water or in two ounces of a watery cornstarch solution (12 ounces of water previously boiled with 2 drachms of cornstarch). The supposed advantage is that "mammoth doses can be taken without gastric upset" (Hanzlik's comment on rectal administration of salicylates is recalled: there is little or no reaction because absorption is poor. When the patient actually absorbs therapeutic doses he cannot avoid salicylism—Ed.).

The prolonged or careless use of cinchophen is felt to be dangerous by Dill³⁰¹. Oxyliodide seems of little value to Meader²⁴¹. The toxic effects of amidoxyl benzoate (ammonium orthoiodoxybenzoic acid) have been reviewed by Bell and Richmond,⁷⁰⁰ who report an instance of fatal poisoning thereby. Cod liver oil (1 to 2 drachms, three times a day), viosterol (10

to 15 minims daily), or halibut oil with viosterol (10 to 15 minims daily) are approved (Dill and others) Hypochromic anemia will be helped by iron only if the disease is relatively inactive (Minot²⁸⁶) Arsenic and sodium cacodylate are still used by some (Buie¹⁹⁰ Seybold,²⁸⁸ Minot, Dill)

Thyroid gland therapy was of real benefit to only 17 per cent of 103 patients treated by Hall and Munroe²⁵⁴ For patients whose history suggests "deficient ovarian secretion" Haggart³⁰⁷ uses amniotin pessaries in conjunction with thyroid extract Endocrine therapy may at times bring about improvement, but according to Brown,²⁹⁰ will rarely completely cure any joint disease

Sodium aurothiopropyl sulphionate (allochrysine) was given intramuscularly in a series of injections to 44 patients by Forestier²⁰⁷ Seventy per cent received a "good" or "very good" result A few toxic reactions were seen stomatitis in 20 per cent, skin reactions occasionally Renal insufficiency is a contraindication to treatment

Octozone (O₈), a new form of concentrated ozone, has been advocated by Parkes³⁰⁸ for its oxidizing effect It is produced by passing oxygen at a pressure of five atmospheres in an "electroniser" It can be administered by mouth, as a skin bath, or by rectal or intramuscular injections

The administration of chaulmoogra oil, after the method of McIlhenny (1931), was used by Hebert³⁰⁹ in 21 cases All but four patients were improved Six to twenty injections of 3 to 5 c c were given into the gluteal region Its oral administration seemed ineffective

A revival of sulphur therapy is current, colloidal sulphur being the favored preparation According to Cavadias (1925), patients with atrophic arthritis exhibit a deficient thiopexy, their cells have lost the ability to retain sulphur As a preliminary to its use in arthritis, Wheeldon and Main³¹⁰ reported on the toxicologic effects of a colloidal sulphur preparation given by intraperitoneal or intravenous injections to rabbits In clinical doses no apparent harm was observed (A few 1934 reports will be analyzed in our next review—Ed)

Colloidal calcium and certain dietary recommendations are prescribed by Aulde,³¹¹ who believes that the basis of arthritis lies in a chemical deviation involving calcium and magnesium

The intra-articular injection of Pregl's solution is suggested by Thomson⁶⁵

Rest, Activity, and Physical Therapy The value of physical therapy and the principles of its application are being increasingly recognized, but are worthy of constant restatement (Coulter,³¹² Ray,³¹³ Buckley,²⁸⁹ ³¹⁴ Kovacs³¹⁵) Rest is looked upon as the most potent single therapeutic procedure at our command, but rest does not necessarily mean bed rest The latter, improperly carried out, may nullify its purposes (Minot) The arthritic patient who must be put to bed or kept physically quiet must not be allowed to remain wholly inactive or increased muscle atrophy, flexions, and other deformities may result (Pern³¹⁶ ³¹⁷ and Munk³¹⁸) A

judicious balance must be made, therefore, between mental and general bodily rest and rest for inflamed joints and muscles on the one hand, and nontraumatizing physical activity on the other. For an acute exacerbation, Anderson²³⁴ feels that a maximum of a week or two in bed is generally sufficient, more may be dangerous.

While the more common types of physical therapy, such as dry heat, diathermy, massage, and exercises, are of great value, the pool bath in which patients may use muscles and joints in the water is of special value and should be more available (Ray,³¹³ Lautman³¹⁹). The "glove bath," a variation in the application of heat for painful hands and feet, is described by Ray³²⁰. The hands, enclosed in rubber gloves or the feet in rubber socks, are immersed in hot water at a temperature of from 105 to 110° F for 20 to 30 minutes daily. Buckley^{-8 289} advises cold baths for robust patients, warm baths followed by brief cold effusions for less robust patients. Prolonged and habitual hot baths lessen the skin's diminished power to react promptly to its environment. The merits of various types of physical therapy are presented. Pistany mud (Schmidt³²¹), infra-red rays, roentgen-ray treatments, and "fever therapy" (Dausset and Lucy³²²).

Roentgen-Ray Treatments The beneficial effects of roentgentherapy in arthritis may, Langer³²³ feels, result from its influence on the vegetative nervous system, disturbances of which are so frequently present. Roentgen-rays first irritate, later quiet this system. He treated 65 patients with atrophic arthritis, 138 with hypertrophic arthritis, and 160 with "mixed types of arthritis." Seventy-five per cent of his patients experienced increased pain for about 48 hours. In 28 per cent this increase of pain was prolonged for one to two weeks and was associated with general malaise. The majority of patients are benefited, although results may not be apparent in some cases for several months. Of 86 patients with marked vegetative nervous system disturbances, 63 were treated only over the corresponding ganglia and nerves, others received both local and articular paravertebral roentgen-ray treatment. The latter plan is preferred, but many of the former group were made so comfortable that local treatment over affected joints was omitted. Coldness and clamminess of extremities, and swelling and pain were diminished. A control series (number not given) treated by other means than roentgen-rays were not so benefited. Sixty per cent of 180 patients with atrophic arthritis treated by Kahlmeter²² obtained marked relief. Scott³²⁴ believes that hypertrophic arthritis and "infective arthritis" are uniformly benefited, but that atrophic arthritis is not. In this Hernaman-Johnson³²⁵ agrees. Douthwaite,³²⁶ however, noted benefit from roentgen-ray treatments in cases of spondylitis with extensive ossification of spinous ligaments.

Fever Therapy In the light of subsequent events it has become the fashion to consider that foreign protein therapy, such as typhoid vaccine intravenously, was the first modern form of fever therapy, although it is not at all certain that fever was responsible for its benefits. Fever therapy is

the "newest" form of physical therapy. Following malaria treatment, fever has been induced by "super-diathermy," radiotherapy, hot air-conditioned cabinets, and hot baths. Markson and Osborne³²⁷ in 1933, and also in 1931, induced by diathermy a temperature of 103 to 104° F. for seven to eight hours in the treatment of "chronic infectious arthritis." One fever session a week was given for eight weeks. In six cases, two patients were "markedly improved," three were "improved," and one was not improved. "Striking results" were obtained by King³²⁸ in an unstated number of cases of both atrophic and hypertrophic arthritis. Relief of pain and increased mobility were noted by all. In some cases a "cure" was simulated. Other patients were only moderately and temporarily benefited. Even "after complete relief has been attained," further fever sessions every few days are advocated by him to prevent recurrences. Speed³²⁹ noted some marked improvements although at times relapses occurred (no figures given).

Carpenter and Warren³³⁰ believe that arthritic patients respond better to fever provoked by diathermy than by radiotherapy. Using diathermy, Bishop, Horton, and Warren⁶⁷ gave 26 treatments to 15 patients with chronic infectious arthritis. Two fever sessions of five hours each were given. Results were "very encouraging" in 63 cases of atrophic or hypertrophic arthritis treated with radiotherapy by Tenney⁶⁸. At the end of eight months, seven patients were symptom-free, 48 were definitely improved, 8 were unimproved. Pope³³¹ favors the use of hot baths or diathermy and noted that at first "arthritics have their pains and stiffness greatly increased." Coulter³³² favors diathermy hyperpyrexia but uses hot baths to lower the cost of treatments. Berris,⁷⁰ using heated cabinets, treated 11 patients with atrophic arthritis with three sessions a week for three weeks. Three patients obtained "complete relief," and the majority were "definitely improved." About 60 patients with atrophic arthritis seen by Simpson, Kislig, and Sittler^{71,332} were each given two fever sessions at 104 to 105° F. for four to five hours by radiotherapy and heated cabinets. Thirty per cent believed they had experienced a complete remission, an additional 30 per cent were "satisfied with the result." Forty-three patients were treated by Kohn and Warren³³³. Only one or two fever sessions were given to each. Benefit was obtained by 35 patients, pain rapidly diminished and mobility of joints increased. Eight were able to earn a living. Relapses within one to two years occurred with three patients who were relieved by further treatment.

Favoring diathermy electropyrrexia, Markson and Osborne³²⁷ reported further results in the treatment of 19 patients. They insisted that eight treatments at a temperature of over 104° F. for eight to ten hours, are required. Of the 10 patients so treated, seven (70 per cent) were benefited, complete relief was noted by one patient for 15 months, one for 21 months, two for 20 months, three were "improved" for 12 to 14 months (end of observation period). Of nine patients treated with shorter sessions (four hours), 56 per cent were improved, five were definitely improved for

three months or longer, three were improved for only one month. In a small series of cases (numbers omitted) Kovacs³¹⁵ noted failures and encouraging results equally divided. Patients with atrophic arthritis do not stand as high temperatures (not over 104.5° F) as comfortably as those with gonorrheal arthritis. Auclair³³⁴ noted complete failure in only seven of 80 cases of various types of "rheumatism" (no details given).

Cecil's²¹⁷ results "have been rather disappointing," and he believes the wave of enthusiasm for hyperthermia in arthritis is not justified. In a limited series (number not stated), no benefit was noted by some, only temporary effects in others, in a few cases improvement was apparently permanent. Kinsella²⁹⁸ noted only temporary relief in an unstated number of cases.

Physiologic effects from fever therapy by various means seem to be about the same. The pulse rate rises to 130 to 150. Blood pressure rises then falls. The electrocardiogram shows contractions of lowered voltage (reduction of amplitude). The leukocyte count may show an initial drop within two hours, and may then rise to 15,000. There is no change or, due to dehydration and concentration, only a slight rise in blood urea, uric acid, sugar, creatinin, and calcium. There is a loss of carbon dioxide with a tendency to a slight alkalosis and an increase in the pH of blood. The most noticeable alteration is that discovered by Simpson and his colleagues: marked loss of chlorides from blood and tissues. Patients lose from 20 to 26 gm of sodium chloride with each session; there is no free hydrochloric acid in the stomach and the blood chlorides fall 40 to 100 mg. Simpson feels that chloride loss in sweat is responsible for symptoms of exhaustion, fatigue, nausea, vomiting, abdominal cramps, and muscular twitching, occurring during and after fever sessions, and that they are all practically eliminated by supplying by mouth large quantities (four to six liters) of chloride-containing fluids, such as iced 0.6 per cent saline solution.

In conclusion, reports to date have in general concerned themselves with small numbers of cases, observed at most for about one to two years. The number of sessions advocated has varied from one or two, to eight, or as high as 20, sessions being given from one to three times a week. Whereas diathermy and radiotherapy were the original methods of choice, there has been a reaction in favor of simpler and less expensive methods, such as heated air-conditioned cabinets. Results have been variable "disappointing" to some, with "87 per cent improvement" and not infrequent "cures" reported by others.

Climate and Clothing Arthritic patients tend to wear heavy underwear and extra clothing in an effort to "keep out" the weather and to protect themselves against thermal and climatic changes to which they do not adapt themselves readily. Light, porous and loose-fitting clothing is preferable (Brown²⁹⁰ and Buckley³¹⁴). Changes in external temperature normally induce a rapid and effective vasomotor response in vessels of the skin. In the arthritic patient, such responses are laggard and incomplete. Flannel and

nonporous clothing tends to induce a sodden condition of the skin and further failure of cutaneous responses. In consequence, the patient feels cold and proceeds to cover himself with yet more flannel, aggravating the condition.

The explanation for the resulting "cold sweat" is given by Brown²⁰⁰. Sweat glands and blood vessels of skin are both under control of the sympathetics. Normally the sympathetic actions on these two structures are in an "inverse direction", stimulation of sympathetics constricts blood vessels but causes sweat glands to secrete. Normally, as sweating occurs with flushed skin vessels, one set of sympathetic fibers is thrown into action and the other set of fibers is inhibited. If both sets are stimulated simultaneously, the "cold sweat" of disease or emotion results.

Clothes which are very porous, with a network enclosing air, are both warmer in winter and cooler in summer because they permit a more adequate cutaneous response.

It is difficult to determine the value of climate in relieving arthritis, as a change in climate is generally associated with the institution of other factors, such as rest and intensive physiotherapy. While no proof is offered by Holbrook¹⁹³ as to the specific role played by climate, he noted definite and sustained improvement in many cases of arthritis of the "last resort type" and dramatic response in others in which treatment was not given by removal of foci, medicines, or vaccines. (Some patients, however, obtained no significant relief and Holbrook has made it clear here and elsewhere that "climate is not a panacea for all chronic arthritis" and that, "without an adequate program of treatment chronic arthritis may continue as a crippling disease even in the Arizona desert"—Ed.)

According to Buckley³¹¹ there is no inherent difference between seaside and inland climate in arthritis, but some seaside places appear to be more unfavorable for both arthritis and fibrositis because of climatic peculiarities not yet identified. Sunshine, per se, has no directly beneficial influence on arthritis, although in moderation it is stimulating to metabolism. Hot climates, and all humid and relaxing climates, are unfavorable to arthritis, and the prevalence of high winds is prejudicial. Buckley feels that arthritic subjects are usually better in cool climates and weather provided they are protected against undue exposure and dampness.

Climate may play a more obvious rôle in the prevention than it does in the cure of arthritis. Since it affects Indians of Montana, Wyoming, and Dakota, but apparently has not affected any of a tribe of 5,000 Indians of the Tucson Desert, Holbrook believes the advantage of Arizona's climate is established. Factors of diet, foci, and so forth, were considered there seemed to be only one variable factor—the climate. Of 1,000 consecutive cases among whites seen by Holbrook, in only one case was the patient a resident of Tucson. Only two local cases were found in the practice of 122 physicians in that locality.

Synovectomy Reduction of pain, and considerable restoration, some-

times complete, of function may follow synovectomy, according to Painter³⁷⁵ and Bernstein³³⁶ who thus treated 4 and 25 patients, respectively. Painter operated in relatively inactive cases, removing the product of previous inflammation which was putting the joints at a mechanical disadvantage by distending the capsule, thus rendering the joint unstable. Bernstein got poor results in cases of multiple atrophic arthritis with lesions of cartilage, but when the latter were not present the results were good.

Sympathectomy Sympathetic ganglionectomy and ramisection was proposed by Rowntree and Adson (1927) for the treatment of arthritis. Favorable results in selected cases were reported by them and others. It has been suggested by some that the operation provided only a temporary increased blood flow to involved regions. Thus Johnson, Scupham, and Gilbert,³³⁷ making plethysmographic studies in a case of atrophic arthritis before and after unilateral cervical sympathetic ganglionectomy and ramisection, noted an early relaxation of blood vessels, but a recovery of independent tone of vessels 21 days after operation. No permanent increase of peripheral circulation was demonstrated, and they felt the postoperative increase in local heat to be due to loss of sweating and evaporation which normally cools the skin. Postoperative chemical changes in femoral venous blood, noted by McMaster³³⁸ in dogs subjected to unilateral lumbar sympathectomy, were a lower carbon dioxide and a higher oxygen content on the operated side, there were no differences, however, in the lactic acid or sugar content. He concluded, therefore, that the changes in volume of the gases in the blood were not of metabolic origin but due to an improved blood flow. Since the chemical differences disappeared after a few months, McMaster believed that physiologic readjustments must take place, restoring the sympathetomized side to an essentially normal state.

Evidence that the flow of blood is actually and permanently increased by sympathectomy is, however, presented by Herrick, Essex, and Baldes,^{339, 340} who noted that the blood flow in the femoral artery of dogs after unilateral lumbar sympathectomy was doubled and remained so for as long as 34 months after operation.

From observations on the healing of experimental fractures in animals subjected to unilateral ganglionectomy, it appeared to McMaster and Roome,³⁴¹ Zollinger,³⁴² and Key and Moore³⁴³ that the operation had but little or no effect in hastening osteogenesis. Cartilage defects produced in dogs by Key and Moore healed as readily on the unaffected as on the operated side, and these workers concluded that their observations offered no evidence, either for or against the use of sympathectomy for arthritis.

Although sympathectomy produced a "curious relief from pain in many instances" in cases of atrophic arthritis seen by Kinsella,²⁹⁸ it did not prove sufficiently valuable in his opinion to justify its continued use. One patient, so treated by Johnson, Scupham and Gilbert, was not relieved and the arthritis progressed. A patient of Peet, Kahn and Allen³⁴⁴ whose pains were relieved only after chordotomy, was unrelieved by previous sympathectomy.

However, "gratifying results" were obtained by one of Kerr's ³⁴⁵ patients with polyarthritis. Spurling and Jelsma ³⁴⁶ reported results in eight cases of chronic arthritis, of 2 to 15 years' duration, in which pain was a dominant symptom. In four cases the lumbar, in one the cervicothoracic, and in three both chains were removed. In seven of the eight cases the patients thought the benefit obtained justified the operation. The results were "highly satisfactory" in cases of periarticular, but with little or no evidence of osseous, injury, results were "reasonably satisfactory" as far as pain relief was concerned in cases of moderate articular involvement and "unsatisfactory" when ankylosis and joint destruction were present. Ten patients were subjected to sympathectomy by Flothow and Swift ³⁴⁷. Seven of these patients were "distinctly improved," especially as to relief of pain. In three cases no significant result was obtained.

Henderson and Adson ³⁴⁸ have reviewed results of sympathectomy for 41 patients with atrophic arthritis treated by them in collaboration with Rowntree, Hench, and Craig. "Marked improvement" was obtained by 20 of the 41 patients. For this group the average age at onset of the disease was 21 years, and the average duration 58 months. Eleven patients obtained but slight improvement, their average age at the onset of the disease was 29 years and the duration of the disease 76 months. In six cases failure resulted, the average age at onset was 28 years and average duration of symptoms 92 months. In cases of long standing disease and deformity, sympathectomy was of no value. Best results were obtained by young patients whose disease was of relatively short duration. In very carefully selected cases the procedure may give distinct relief.

All workers agree that the suitable case is that of a young patient who has cold, clammy extremities, whose arthritis is only, or chiefly, in the hands or feet, and in whom marked articular change has not yet occurred. While mobility may be increased and swelling reduced, the relief of pain is the chief result. Suitable cases can be accurately selected by noting whether or not temporary relief follows trial injections of acetylcholine hydrobromide (Spurling and Jelsma ³⁴⁶), novocain, or use of other strong vasodilators (Flothow and Swift ³⁴⁷).

Histologic studies have been made by Craig and Kernohan ³⁴⁹ of sympathetic ganglions removed from 46 patients who had arthritis. Although changes were seen, they were comparable only to those found in ganglions removed at necropsy from patients unaffected by arthritis or by derangements of the sympathetic nervous system. Nothing was found therein to explain the vasomotor disturbances of arthritic patients. They concluded that the noxious agent causing the disease does not act directly on the sympathetic ganglion removed, but since removal of such ganglions frequently leads to improvement of blood supply to the affected limbs, it would seem that the ganglions act simply as relay stations for impulses from higher centers affected by the disease.

Chordotomy. A man, aged 20 years, who had atrophic arthritis of

three years' duration, suffered severe pain in an arm, shoulder, and in the lower extremities. This pain was not relieved by usual measures or by sympathectomy, but it was almost completely relieved following bilateral cervical chordotomy, by Peet, Kahn, and Allen³⁴⁴. Pain was abolished without risk of respiratory paralysis by sectioning the tract at the third cervical segment on one side and approximately the eighth cervical segment on the other. (The patient had no pain when lying in bed, according to a personal communication from Kahn, but had "excruciating pain" on attempted motion of knees. In acute arthritis or acute exacerbations of chronic arthritis there may, for a matter of days or a few weeks, be considerable pain particularly on motion, even so, some relief is practically always afforded, at least temporarily, by the usual measures. When chronic intractable pain occurs in "chronic rheumatism," and when narcotics are required, the admonition of Ryneerson and Hench (1931) to "suspect malignancy in 'chronic rheumatism' requiring morphine" is in order. Although chordotomy was well borne and succeeded in its purpose in this case, it would seem to be a very radical procedure, and one that is rarely indicated—Ed.)

Acupuncture Analgesia lasting three to four days can be provided in the majority of cases of painful arthritis by acupuncture, an old remedy still favored by Ferreyrolles³⁴⁰. Relief is not dependent on anesthesia, as analgesia can be obtained using empty needles.

Splenectomy Chronic atrophic arthritis is frequently associated with anemia and with adenopathy, less frequently with hepatomegaly and splenomegaly. While the syndrome of chronic arthritis, splenomegaly, and leukopenia may represent either "adult Still's disease" or the coincidental association of arthritis and early Banti's disease, Felty (1924) believed it represented a distinct clinical entity. Hanrahan and Miller³⁴¹ performed splenectomy in such a case—the patient being a woman, aged 50 years, who presented an atrophic arthritis of 5 years' duration, an enlarged spleen, palpable liver, anemia (3,450,000 erythrocytes), and a leukopenia (800 cells) with a relative lymphocytosis (86 per cent). Culture of the spleen was negative after 5 days. It weighed 525 gm (normal, 150 gm). Hyperplasia of endothelial cells lining dilated sinuses, and increased numbers of plasma cells in the pulp spaces, were seen. A specimen of liver at biopsy revealed fatty changes in the central zone and moderate round cell infiltration along portal vein radicles, limited to the periphery of the lobule. Within three weeks of the operation the patient noted improvement. Four months later, she was still much improved, anemia was not present and the leukocyte count was 10 000 per cubic millimeter.

It is recalled that Chauffard, in 1896, and Herringham, in 1909, called attention to the association of arthritis in adults with splenomegaly and hepatomegaly. Anemia was not emphasized. In 1897, Still noted arthritis in children with anemia, enlarged lymph nodes and enlarged spleens, but he did not mention hepatomegaly. Others have since reported cases of arthritis associated with various types of reticulo-endothelial response, with

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leukopenia or leukocytosis While it is well to point out such variations, it seems unwarranted to give each combination a new name (Hench³⁵²) It is not clear whether these reactions represent a complication or a defense mechanism on the part of the reticulo-endothelial system If the lymph nodes are the first line of defense and the spleen and liver the second defenses, Hench believes one should think twice before advising splenectomy Only temporary benefit was noted by him in one such case, probably the nonspecific temporary improvement any surgical operation may provide (For another such case see also Craven, E B Jr Am Med Assoc, March 17, 1934) The adenopathy and splenomegaly would seem to Hench to support the infectious theory, for such tissue responses whether they are complications or defense reactions, are more suggestive of reaction to infection than to a metabolic or endocrine disturbance (In connection herewith should be considered two cases of lymphatic leukemia producing symptoms like rheumatic fever, they will be described later —Ed)

Periarticular Bone Puncture An elderly woman, who had long suffered with an atrophic polyarthritis which had been unrelied by periods of rest, fell and fractured a femur After the bone healed Mackenzie (1931) noted that the patient's arthritis was no longer painful Recalling that in atrophic arthritis pathologic changes are present in bone and bone marrow as well as in articular structures, Mackenzie pondered on the possible benefits of deliberate "experimental bone fracture" or bone punctures He instituted the procedure in more than 60 cases, with interesting results³⁵³ An opening is made with a large bit, or a $\frac{3}{4}$ inch trephine, into (for example) the lower end of the femur and upper end of the tibia Bone marrow flows out like thin oil, due probably to fatty degeneration of marrow Marked relief of pain, increased joint function, and increased erythrocyte count were noted In some cases the procedure seemed to be "curative"³⁵³ (Charbonnel, in Bordeaux, has reported similar results in one case, 1933)

Reconstructive Surgery In most patients chronic arthritis sooner or later reaches the stage of quiescence A fortunate number will have little or no deformities, or deformities of but little significance Some may have one or two joints seriously deformed, others are grievously deformed and appear "hopelessly crippled" At the hands of the skilled orthopedist much can be done to restore hope, motion to the joints, and a means of livelihood What can be done and the optimal time for doing it are matters of great importance to the physician in attendance The indications for any methods of orthopedic reconstruction of such joints are again set forth by Wilson and Osgood,³⁵⁴ and by Stump^{355 356} Reconstructive surgery should not be undertaken until the joints have been free from active disease for at least six months It is at times difficult to determine whether activity has ceased

fibrosed capsule, or to strain on an injured joint. The problem of correction is a difficult one for the patient who may have to endure long hospitalization and multiple operations, but treatment is amply remunerative.

Remissions, Usual and Unusual The course of atrophic arthritis is characterized by exacerbations and remissions. The more common causes of exacerbations are overactivity, weather changes, the menses, and intercurrent infections such as colds and influenza. "Natural remissions" follow rest and the onset of warm or stable weather. The latter months of pregnancy may be accompanied by a marked recession of arthritic activity.

Remissions, unfortunately too often temporary, are induced by many types of treatment as these pages indicate, but the true value of any treatment must take into account natural remissions. Typhoid vaccine may produce a remission, sometimes short lived, sometimes prolonged. Wilberforce³⁰⁷ noted a case, of a woman of 57 years with advanced painful deformities, in which a striking remission set in during an attack of typhoid fever and lasted more than a year. Many have noted remission induced by relatively unrelated surgical procedures (Kinsella²⁹⁸).

A "new cause" of remissions has been reported by Hench³¹⁸ who made observations over a period of four years on the effect of intercurrent jaundice on the rheumatism (arthritis, fibrositis, sciatica) of 16 patients. In some cases the jaundice had been induced by cinchophen, in others however, it was unrelated to drugs. Coincident generally with the onset of jaundice, 14 of the 16 patients obtained partial, or more usually, complete relief of pain for variable periods of several weeks to many months, and in some cases even years. In several cases marked, even complete, reduction of swelling was noted. To this observer the therapeutic implications seem obvious, it would be gratifying if one were able to repeat nature's miracle, to provide at will a similar beneficence by the use of some nontoxic accompaniment of jaundice effective in available concentration. (These observations have been confirmed by Sidel and Abrams, *New Eng Jr Med*, 1934, ccx, 181-182—Ed.)

Prognosis and Results of Treatment Many patients, indeed many physicians, have the impression that "nothing can be done for atrophic arthritis." This pessimistic point of view is wholly unjustified, as statistics show. The foregoing pages indicate that success rarely follows the institution of one simple form of treatment. The disease does not rapidly fade as the result of one therapeutic tour de force. The patient must be taught the importance of the multiple aspects of his disease and its treatment. He must appreciate that a long period of training is necessary. But he can generally be assured that wisely conducted treatment, based on a composite program comprehensively applied, leads to success (Minot²⁶⁸).

Beneficial results follow the isolated use of many of the approved methods of treatment in from 50 to 70 per cent of the cases. When a number of measures are instituted, notable improvement and reasonably early cessation of the disease occur in 70 to 80 per cent of cases. In Lipkin's²⁰⁶

series of 200 patients with chronic arthritis, 21 per cent had "recovered," 32 per cent had marked and 20 per cent moderate improvement. In Matz'¹⁹² series, 76 per cent were "improved." Minot cites figures from Sweden and from London to the effect that within three years 60 per cent or more of all patients were working comfortably at their old jobs. Of 50 patients (half with atrophic and half with hypertrophic arthritis) who followed Minot's²⁸⁶ instructions faithfully for four years, 85 per cent were definitely better and in 60 per cent the disease had apparently been arrested for two years or more. This was in contrast to results for those who did not follow treatment faithfully, of whom only 35 per cent seemed to be definitely better.²⁸⁶ Osgood¹⁸⁷ believes that chronic arthritis is a controllable disease, and that there are few chronic diseases for which more can be done. Such high percentages of recovery or arrest can "certainly not be attained with cancer, almost certainly not with chronic heart disease, and probably not with chronic tuberculosis," the three most common chronic diseases in his state.

HYPERTROPHIC ARTHRITIS

It has been explained that the term "hypertrophic arthritis" as used herein refers to the clinical syndrome sometimes designated senescent arthritis, degenerative arthritis, or osteo-arthritis. It signifies a disease entity and not a roentgenographic pattern also seen in certain stages of traumatic, gouty, hemophilic, gonorrheal, or other types of arthritis, including even the late stages of atrophic arthritis, especially in weight-bearing joints. It has been stated that although some (Willcox,¹⁹⁸ Knaggs,¹⁹⁷ Clawson and Wetherby,²¹⁰⁻²¹¹ Smith²⁷⁶) believe it is but a variation of the disease which in younger or less robust individuals is manifest as atrophic arthritis, the majority insist that it is a separate entity, differing in cause, in clinical, immunologic, pathologic, and roentgenographic features, in treatment and response thereto, and above all in prognosis. Unlike a squeaky wheel, the creaky joints of hypertrophic arthritis do not get as much attention as the generally less noisy but more painfully diseased joints of atrophic arthritis. Few articles concern hypertrophic arthritis alone, we learn of it as its contrasting relationships to its more potent cousin are mentioned, or when it is used in series as a control for atrophic arthritis.

Symptoms and Course. Its clinical, pathologic, immunologic, and roentgenographic characteristics have thus already been briefly touched on. For a fuller summary reference can be made to the Primer.¹⁸⁸ In hypertrophic arthritis, prodromes are not so common or striking, for here we are not dealing with a toxemia with its widespread manifestations, or at least if a toxemia is involved it is much less formidable and the disease's manifestations tend to be peculiarly localized. Such premonitions as there may be, Painter²⁶⁷ feels, include the following lassitude, headache, sluggishness of intestinal activity, and frequency of micturition, suggesting an impaired digestion and a disturbance of metabolism. Many of the women in Lipkin's

series noted nervousness, dizziness, tingling of fingers, hot flashes, and other "menopausal symptoms" Thirteen women exhibited Heberden's nodes, the earliest at 36 years of age Only one man had such nodes The lumbar spinal column and knees were involved next in frequency, and the cervical spine, shoulders, and hips were less frequently attacked Only half as many (53) patients with hypertrophic arthritis consulted Lipkin as those with atrophic arthritis (113 patients)

In Matz' series there were more cases (213) of hypertrophic than of atrophic (172) arthritis Each of the patients in the former had an average of 2.8 involved joints as compared to 3.7 joints in the atrophic group Only 15.5 per cent of those with hypertrophic arthritis gave a hereditary or familial history of joint disease The disease may manifest itself much earlier than is generally supposed, according to Matz, in whose series the average age of onset in 213 cases was 31 years Forty-five per cent were above, 23 per cent below standard weight Constipation was generally absent Fifty-three per cent gave a history of focal infection (as compared to 83 per cent in the atrophic cases) In 26 per cent of cases the onset of symptoms was acute The average number of attacks was 2.7 per patient, although half of them had only one attack The average duration of the disease was 132 months (From some of these statements it seems likely that at least some of the cases included were roentgenographically but not clinically of the hypertrophic type—Ed.)

In Eaton's series more women (76) than men (47) were painfully affected Although about 23 of 123 patients noted pain between the ages of 20 and 40, the majority were attacked between the ages of 40 and 60 Many patients with Heberden's nodes remarked on a familial tendency thereto Only about 14 per cent were underweight, 50 per cent overweight Quite a number lost weight during their illness Vasomotor phenomena, such as "dead fingers," patchy erythemas, urticarial wheals, and the symptoms of nervousness, restlessness, excitability, loss of mental vigor, and exaggeration of tendon reflexes, were noted and were more frequent among women than men affected with hypertrophic arthritis, they were not present, however, as often as in cases of atrophic arthritis Sweaty skin was seen more often among men, but less frequently in both sexes than in cases of atrophic arthritis The disease involves wrists, elbows, and ankles much less frequently than does atrophic arthritis Eaton²⁰⁰ and Ray³⁵⁹ have reviewed its characteristics at its favorite sites of predilection A painful great toe, with hypertrophic changes, may be the analogue of a Heberden's node (Ray)

The hip is fortunately not involved as often as fingers, knees, and spine, but when attacked it is likely to cause more disability Of 302 hip joints of persons more than 20 years of age who were studied roentgenographically for various diseases by Brailsford,³⁶⁰ 203 showed arthritis "osteoarthritis" in 130 cases, "chronic arthritis" (atrophic?) in 73

Roentgenographic Picture The studies of Scott²⁰¹ and Rigler and Wetherby²⁰² have been commented on (p 1498)

Pathologic Changes, Joints The characteristic pathologic changes—cartilage fibrillation and degeneration, osteophyte production and destruction, and eburnation of subchondral bone—have been reviewed by Eaton Knaggs' ¹⁹ opinion regarding the pathologic discreteness of the disease has also received comment (p 1501)

Pathologic Changes, Nodes It has been noted that subcutaneous fibrous nodes are not to be expected in hypertrophic arthritis (p)

Laboratory Data, Blood Counts, Blood Volume, and Blood Chemistry In his studies on blood in arthritis Eaton included both atrophic and hypertrophic types without distinction Since abnormal counts were found in all but three of 250 cases, we are left to assume that changes in cells in hypertrophic arthritis are consistently present and similar to those in atrophic arthritis (This is not the usual belief and it is unfortunate that the types were not studied separately—Ed) The filament-nonfilament count may be altered in hypertrophic, as well as in atrophic, arthritis, but it is much more likely to be normal in the former and rarely if ever normal in the latter (Stembrocker and Hartung ²¹⁴) The blood volume (generally above normal in atrophic arthritis) was found by Sparks and Haden ²¹⁸ to be 67 per cent below the average normal in 15 cases of hypertrophic arthritis, probably because of associated obesity As we have noted, the phosphatase test is apparently normal (Race ²²¹), and the sedimentation rate is either normal or but slightly elevated, 20 to 30 mm in one hour (Dawson and Boots ²¹⁰) In certain cases it may approach values more frequently seen in cases of atrophic arthritis (Oppel, Myers and Keefer ⁶²)

Routine studies of blood chemistry in cases of hypertrophic arthritis show no significant changes in serum calcium or phosphorus, in calcium and phosphorus metabolism (Bauer, Bennett and Short ²²⁰), or in blood sugar, urea, or creatinin Some (Eaton ²¹⁹) report a tendency to high normal or slightly elevated values for blood uric acid

Etiology and Pathogenesis Opinions on the cause of hypertrophic arthritis are that it is due to (1) infection, (2) degenerative process of age, (3) trauma, (4) a metabolic disturbance, (5) an endocrine disturbance, and (6) circulatory disturbances associated with arteriosclerosis or other causes Age and trauma are the factors most often incriminated, and those who believe it is an infectious disease are in the minority Indeed, positive findings in the voluminous studies used to support the infectious theory of atrophic arthritis gain their chief distinction in that similar studies in hypertrophic arthritis are generally negative Thus, blood or joint cultures in hypertrophic arthritis were found to be negative in 27 cases by Gray, Fendrick, and Gowen, ^{107 108} as they have been in general by others There was practically no agglutination of streptococci in these cases, nor in about 60 cases seen by Dawson Olmstead, and Boots, ²²⁰ nor in 44 cases studied by Nicholls and Stansby ^{201a} Only 15 per cent of 28 cases seen by Keefer, Myers, and Oppel ¹⁴⁰ exhibited streptococcal agglutinins In 23 cases tested

by the latter with streptococcal nucleoproteins, skin reactions were negative in 63 per cent, slightly positive in 37 per cent

In spite of these findings, several workers favor the infectious theory. Thus Crowe^{361 362} feels that trauma and deformity are not very important predisposing factors, and Ray³⁶³ believes that while age and trauma play some part, hypertrophic arthritis is "undoubtedly associated with the absorption of toxins from a sluggishly acting bowel." Streptococci are blamed by some (Burbank, Crowe, Clawson, Wetherby, Ryerson, Willcox) on the basis of skin tests, complement fixation tests and occasionally positive blood cultures. Others (Elmslie,³⁶³ Smith²⁶) are less specific and state the belief that it is due to bacterial or food toxins of intestinal or other origin. Thus, while admitting that there is little or no proof that bacterial infections can cause osteo-arthritis, Elmslie feels that they can initiate changes which, altered by other factors, eventually simulate osteo-arthritis. Ryerson believes infected teeth are the chief focus in cases of hypertrophic arthritis.

As causative factors, age and trauma are generally considered cooperative and not regarded separately. Thus, Miller¹³³ and others consider "age" merely the opportunity for mild, long-continued trauma of posture, occupation, and recreation. The radiologic and symptomatic manifestations of hypertrophic arthritis have long been correlated with the decades between 40 and 70, roentgenologic changes being noted rarely before 40, generally between 45 and 50, universally after 60, with symptoms often remaining absent or not appearing until some months or longer after radiologic alterations. Just as symptoms may lag behind roentgenologic changes, so the latter lag behind earlier but unmistakable pathologic changes, as shown by Keefer³⁶⁴ who studied 100 consecutive knee joints of 67 men and 33 women at necropsy. Gross changes identical with those of hypertrophic arthritis were not seen in any of six cases in which patients had been between the ages of 1 and 29, but were seen in 66 per cent of six cases between 30 and 39 years, in 100 per cent of nine cases between 40 and 49 years, in 95 per cent of 20 cases between 50 and 59 years, in 100 per cent of 28 cases between 60 and 69 years, in 94 per cent of 19 cases between 70 and 79 years, and in 91 per cent of 12 cases in which patients had been more than 80 years old. The most frequently involved surfaces of the joint were those of contact. Thus the sites of change were as follows: patella in 81 cases, interpatellar groove in 65, lateral tibial condyle in 64, medial tibial condyle in 55, medial condyle of the femur in 50, and lateral condyle of the femur in 41. Keefer concluded that hypertrophic arthritis is due to aging of joint tissues, but that the lesions produced thereby may be exaggerated by trauma, hemorrhage, infection or urate deposits. (It is unfortunate that these interesting studies were not correlated with clinical data on presence or absence of joint pain—Ed.)

The trauma which produces hypertrophic arthritis may be of the mild, long-continued variety from strains or minor injuries from mechanical or anatomic derangements, for example, in the hip (Elmslie), or it may be of

the more acute type Young Olympic athletes frequently exhibit osteophytes in the joints most used (Miller¹³³)

Pemberton believes that hypertrophic arthritis, just as atrophic arthritis, may be due to defects in peripheral circulation and derangements of metabolism Alterations in peripheral blood flow and in configuration of the colon are noted by him in both types, and while the two should be separated in consideration of symptomatology, pathology, and prognosis, they may be somewhat closely related etiologically and therapeutically Goldhaft and Pemberton (1930) previously produced pathologic changes, chiefly of hypertrophic but also of an atrophic type, in the patellas of dogs subjected to ligation of the patellar arteries To them it is difficult to see why, in man, atrophic arthritis should largely appear in middle life and hypertrophic arthritis later unless these diseases represent different age responses to perhaps identical exciting factors The ligation experiments were repeated³⁶ on dogs of various ages, to note the influence of age in modifying response to a single insult Hypertrophic arthritis was produced slightly or not at all in young dogs, but was produced in mature dogs Thus age seems to govern response to the more direct agent, the vascular insult

In view of these experiments in which hypertrophic changes are subsequent to diminution of arterial blood supply, those of Bernstein³⁶⁶ are of interest Venous congestion of the lumbar spine was produced in five dogs by ligating the lumbar veins After two years, new bone formation on the vertebral bodies, but not on the margins, and cartilage proliferation were noted In one dog passive congestion of the knee joint was produced by ligating branches of the femoral vein Nine months later the synovial membrane showed granulation tissue and pannus formation over articular cartilage, with necrotic areas in the cartilage

Heberden's nodes develop, according to Elliot,³⁶⁷ from the predisposing factors of disturbed circulation and disturbed calcium metabolism, with trauma acting as an aggravating factor (While predisposing and aggravating factors are noted, the inciting factor is not noted) As stated previously (p 1515), the skin temperature is reported as sometimes being lowered and the capillary blood flow slowed in cases of hypertrophic as well as of atrophic arthritis Constriction, tortuosity, and a diminished number of capillaries are seen less frequently in cases of hypertrophic arthritis (Kovacs, Wright and Duryee²⁶³)

Elliot believes that exacerbations of pain and tenderness in Heberden's nodes are related to intestinal irregularity, and that absorption of bacteria or their products is favored by elongated atonic colons We have noted Eaton's observation that no differences could be noted in the eating habits of patients with hypertrophic or atrophic arthritis or of nonarthritic persons

Because hypertrophic arthritis so frequently appears in women about the time of the menopause, it has been called menopausal or climacteric arthritis, the inference being that it is of endocrine origin With others, Miller¹³³ believes that the menopause is not the chief factor but that obesity which may

go with it is, and that "menopausal arthritis" is in reality hypertrophic arthritis from the trauma of obesity. Ellman²⁹¹ approves the endocrine hypothesis. According to Duncan,³⁶⁸ hypothyroidism may be associated with and aggravate hypertrophic arthritis. Stigmas of hypothyroidism were seen by Hall and Munroe²⁵⁴ more often in hypertrophic than in atrophic arthritis. In 108 cases of the former, metabolic rates were below — 10 in 50 per cent, below — 15 in 34 per cent.

Experimental hypertrophic arthritis can be produced, as shown by Key,^{36 369} by a wide variety of methods in which articular cartilage is injured, primarily by mechanical, chemical, or thermal agents or secondarily by functional trauma in a disorganized joint in continued use. The pure functional and senile theories are inadequate, however, as clinical data show, and no one has found the cause of the primary injury to articular cartilage that initiates hypertrophic arthritis in man.

Conclusions on Etiology From the radiologic standpoint there are several kinds of hypertrophic arthritis that associated with Charcot's disease, hemophilia, gout, Paget's or Perthe's disease, acute or chronic trauma, or with infections. Excluding these factors, there remains the group under discussion, the clinical syndrome of "hypertrophic arthritis." The exact cause of this hypertrophic arthritis is obviously not known, but it is predicated largely on age, incited or aggravated by a variety of traumas, and perhaps is secondarily influenced by infection.

Treatment of Hypertrophic Arthritis Many believe, as does J. L. Miller, that the most important part of treatment is to explain to the patient the difference in the prognosis of the disease he actually has from that he thinks he has, and that hypertrophic arthritis (unlike atrophic arthritis which the patient fears) is essentially not an ankylosing, severely crippling, progressive disease. This done, many patients will ask for no other treatment but will bear their difficulties philosophically.

Removal of foci is believed by most to be of no real value in altering the course of the disease (Allan,³⁷⁰ Miller¹³³). Sinus infections, however, were treated by Hurd^{272 273} with reported benefit to joints in this type of arthritis also. Miltner and Kulowski²⁸³ found infected foci in 95 of 100 cases, especially infected teeth, but removal of foci resulted in no improvement in 91 cases, some improvement in nine, and a "cure" in none. Haden²²⁸ concedes that infected foci should be removed as a matter of general principle without expecting specific results.

When obesity is present, a weight-reduction diet is generally advocated to reduce trauma therefrom (Miller¹³³). Ray agrees with Pemberton on the value of avoiding unnecessary metabolic burdens and favors a diet low in calories even in the absence of obesity. On the grounds that the blood uric acid is likely to be high (a disputed point), he urges restriction of purine and the use of supposed intestinal antiseptics (guaiacum and sulphur Bulgarian soured milk). Colonic irrigations are used by Smith²⁷⁶. A diet high in vitamin B low in carbohydrates, but adequate in protein is favored

by Elliot³⁶⁷ Most workers consider diet of minor importance in this type of arthritis unless obesity is present

Vaccines are used by several (Burbank,²²¹ Crowe,⁷⁶¹ Thomson,²⁹⁰ and Ryerson²⁶⁹) Of 245 patients treated by Crowe and Young²⁹⁴ with vaccines and by removal of foci, 7 per cent became symptom free, 33 per cent were "much improved," 46 per cent "improved," and 14 per cent were unrelieved In a later report of 125 patients with osteo-arthritis of the hip, Crowe reported 56 per cent were benefited by such treatment Progressive changes were presumably halted and pains relieved Thomson also used Crowe's vaccine with benefit Clawson and Wetherby used their vaccine for both types of arthritis, indiscriminately Dawson and Boots, and Holbrook and others see no excuse for vaccine therapy in hypertrophic arthritis

Endocrine Therapy Thyroid therapy by Hall and Munroe²⁰⁴ seemed to assist other measures in bringing relief to 49 per cent of 116 patients Possible stimulation of pelvic organs may in part be responsible for the relief obtained by Robinson's²⁷⁰ patients with degenerative arthritis and endocervicitis who were treated by pelvic diathermy and ionization

Physical Therapy The usual methods of heat, massage, and mild exercises are approved A judicious ratio between rest and moderate activity is generally advised, with a little more emphasis on rest and the use of crutches, canes, or caliper splints as necessary to reduce trauma to involved hips or knees (Ray,¹⁰⁰ Miller¹¹³) Manipulation is favored by Douthwaite³⁴⁶ for certain affected hips, but it is decried by Crowe who also does not favor massage or calipers For stimulating circulation in Heberden's nodes Elliot³⁰ advises violin playing or similar use of the hands and he reports the reduction of nodes by the pressure of adhesive or other plaster, bandages, or metallic bands intermittently applied

Roentgenotherapy Radiologic treatment for hypertrophic arthritis in various joints, especially the spine and hips, is favored by several (Kahlmeter²⁷) Langer¹⁷ treated 138 such patients, with reported benefits Scott³⁰¹ believes that poor results have been due to improper dosage Treatments by roentgen rays are the method of choice of Watt,³⁷¹ Hernaman-Johnson,³²⁷ Kempster,³⁷⁷ and Batten³⁷³ Forty per cent of 194 patients were symptomatically cured or "markedly relieved", 23 per cent were "improved," 37 per cent were not (Watt, see Scott³²⁴)

However, in some cases improvement is not lasting (Douthwaite³⁴⁶) Ten of 24 patients with hip disease got considerable relief of pain for six months, but then suffered a relapse Five, however, were remarkably relieved from one and a half to two years Hips seem to respond better than other joints of 10 patients whose fingers were treated by Douthwaite, none were relieved Of 10 with painful knees three were relieved While some believe roentgenograms show improvement (Hernaman-Johnson³²⁷), others see no change (Woods,¹⁷⁴ Douthwaite)

Surgical procedures are rarely indicated, when necessary, they may give

relief Groves,³⁷⁵ has outlined the indications for cheilotomy (removal of osteophytes), arthroplasty, arthrodesis, excision, or osteotomy. Cases of monarticular hypertrophic arthritis in which Bernstein³⁸⁶ performed synovectomy were among those in which "best results" were obtained.

SPONDYLITIS

Backache and Spondylitis Backache, particularly low back pain, may arise from a number of causes of which arthritis is the most common. Atrophic or hypertrophic arthritis of the spine was the cause of "backache" in 46 per cent of 500 cases seen by Duncan³⁶⁸ and of 36 per cent of 668 cases seen by Shands and Oates.³⁷⁶ The differentiation of the types and causes of backache, with details of the examinations necessary, have been considered by several (Bankhart,³⁷⁷ Ely,²⁴⁸ Durham,³⁷⁸ Brailsford,³⁶⁰ Wheeler,³⁷⁹ Moore and Kyle,³⁸⁰ Holbrook, Jepson,³⁸¹ Nicola³⁸²). Conditions from which arthritis must be distinguished as the cause of backache are "sacro-iliac strain or displacement," lumbosacral strain, acute and chronic lumbar strain, "neurotic spine," the "constitutional or structurally weak back," "kissing spinous processes," true lumbago, Pott's disease, fractures, spondylolisthesis, congenital anomalies, cord tumors, and malignancy. It is beyond the scope of this review to discuss such differentiation. Next to arthritis in frequency, painful backs are due to the constitutionally weak or mechanically defective back as found in the woman who, for years, feels comfortable in bed but develops a progressive backache during the day, continues to show no roentgenographic alterations, but is found to have weak back muscles that favor a constant posture of chronic spinal hyperextension. Thirty-four per cent of Duncan's 500 patients suffered therefrom. (Many would argue that postural joint strain is a much commoner cause of backache than arthritis and that postural back strain precedes localized traumatic arthritis in the lower spine in a high percentage of cases—Ed.)

According to Bankhart, patients who suffer with long continued backache almost invariably develop a "neurotic spine," a neurosis superimposed on genuine organic or structural disability. It may vary in degree from a more or less diffuse hyperesthesia to a profound neurasthenia. Its characteristic features are superficial and variable tenderness in contrast to the constant and definitely localized pain of the associated organic condition.

Several have reiterated the well-known fact that while a roentgenogram is absolutely essential, it does not always reveal the cause of back pain. The majority of such sufferers have real trouble, and are not malingerers, but their trouble may not cast a roentgenographic shadow. Roentgenograms of painful backs must be subject to most careful interpretation, as much liping may be present without symptoms, and vice versa. Even when alterations are noted in the roentgenogram they may not be the cause of the backache.

Types of Spondylitis The present tendency is to place several described varieties, excluding special forms (tuberculous, typhoid, and so forth)

under two headings atrophic spondylitis and hypertrophic spondylitis. Atrophic spondylitis is synonymous with the British Committee's ³⁸³ term, spondylitis ankylopoietica, and probably includes the forms called "spondylose rhizomelique," "Marie-Strumpell type," spondylitis ossificans ligamentosa (Knaggs ¹⁸⁷), and "infectious spondylitis." It probably compares with atrophic arthritis in other joints. It is characterized by osteoporosis of vertebrae, often early osteoporosis and destruction of sacro-iliac segments, secondary ossification of ligaments, and ankylosis producing the "bamboo-spine." Early roentgenograms may show little or nothing but atrophy of bone. Later, density of affected facet areas and sharply defined shadows along the course of ligamenta flava may be seen. Still later, small osteophytes and bony ankylosis occur. Those who wish to distinguish the variety in which the anterior common and other ligaments are early and strikingly ossified, separate it from the general head of atrophic spondylitis.

Hypertrophic spondylitis (senescent spondylitis, spondylitis osteoarthritica, von Bechterew type, degenerative arthritis of the spine) is comparable to hypertrophic arthritis elsewhere and is characterized by early, and sometimes gross, lipping of vertebrae with formation of exostoses from vertebral bodies and processes. Knaggs has separated a type or subtype as spondylitis muscularis, which is characterized by kyphosis, immobility, weak muscle tone, not much pain or tenderness, and atrophy of intervertebral disks with eventual lipping and spurring of vertebral margins.

Of the 243 cases of spondylitis studied by Shands and Oates,³⁷⁶ 32 per cent were of the atrophic type. Of these 78 cases, in 12 there were clinical signs and symptoms but negative roentgenologic findings, in 50 atrophy of bone and blurring or haziness about facets and intervertebral disks, and in 16 ligamentous calcification (Marie-Strumpell type). Sixty-seven per cent were of the hypertrophic type, one being of the von Bechterew variety and the rest of the "true type." Of the total group 58 per cent of the patients were men, 42 per cent women. Of the patients with atrophic arthritis, 56 per cent were women, and of those with hypertrophic arthritis 41 per cent were women. The earliest lesions are in the lower portion of the spine, thus the average age of patients with sacro-iliac and lumbosacral involvement at the onset of the condition was 33 years, for those with thoracic and lumbar involvement 42 years, and for those with cervical involvement 46 years. Trauma seemed to be a factor (40 per cent) when the lower regions were involved, but was less so (22 to 24 per cent) for the two higher regions, rarely was it a factor in cases of the Marie-Strumpell type. Pain projection was much more common among patients with cervical (64 per cent) and sacro-iliac (65 per cent) involvement than for those with thoracic involvement (20 per cent), and it occurred in 43 to 48 per cent of cases in which the lumbar or lumbosacral regions were attacked. When the cervical area was involved, marked symptoms were often present without signs. The reverse applied when the lower regions were affected.

Three types of spondylitis are recognized in the study of Holbrook,

Stecher, and Hayden³⁸¹ "primary spondylitis," types A (without ankylosis) and B (with ankylosis), and hypertrophic spondylitis, included with other varieties of generalized hypertrophic arthritis. Type B is considered as identical with Knaggs' spondylitis ligamentosa ossificans. They looked on type A as an unrecognized syndrome, characterized by its appearance in young men, and progressing from an insidious onset to a poker spine, with negative roentgenograms of the spine but with destruction of cartilage and fusion at the sacro-iliac joints. (In many cases of atrophic spondylitis, roentgenographic alterations, aside from or including bone atrophy, may be long delayed. Is not this "new syndrome" but a recognized variant of atrophic arthritis?—Ed.)

Of 386 patients with atrophic and hypertrophic arthritis, 60 were found by Bisgard³⁸⁵ to have hypertrophic arthritis of the cervical spine, with localization of the lippling to the fifth, sixth, and seventh cervical vertebrae in most cases. Thirty-one had occipital or suboccipital headaches, at times, which were made worse by damp, cold weather. Thirty-eight had pain, tenderness, or stiffness in the neck or a sense of fatigue in the neck and shoulders. Eight had neuralgic pains ("neuritis") in shoulders or arms, but radiation was generally not segmental. Sensory disturbances (tingling, burning, or numbness of arms) were present in nine cases (in only two of which was the distribution along nerve roots or trunk), only four patients had motor disturbances (muscle weakness). Atrophy of muscle in arms, or at thenar and hypothenar areas, was occasionally seen. One patient had associated hiccups. Many patients with extensive cervical arthritis, however, are free of symptoms.

A particularly resistant and progressively painful spondylitis must always be suspected of being the result of vertebral malignancy. A man fell and a "backache" developed which persisted for 18 years. He then experienced severe and constant low back pain which was unrelieved by the usual treatments and required morphine. An adenocarcinoma was found by Mason-Hohl³⁸⁶.

Etiology The same theories apply here as to arthritis elsewhere, with recognition of the fact that trauma plays a particularly active part in any arthritis of the spine. Ely²⁴⁸ insists that hypertrophic spondylitis is due to "some living organism not bacterial, which usually gains access to the body through the open bone at the roots of dead teeth." Its later habitat is probably the intestines. He conceives the primary pathologic change to be an aseptic necrosis in bone marrow near joints, and that the ensuing arthritis is essentially traumatic. Diverticulitis may be a common cause of spondylitis, according to Brailsford³⁸⁰ who cited statistics of others as follows: of 100 patients with diverticulosis, 72 had spondylitis, of 100 patients who did not have diverticulosis but who were of the same average age (58 years) only 20 had spondylitis.

Treatment The treatment in general is the same as that described for atrophic or hypertrophic arthritis, with braces and corsets as necessary.

For painful cervical arthritis Bisgard favors immobilization in a Thomas collar for several weeks with daily traction, and also roentgenotherapy. Rest is not advised by Pockley³³ in cases of "kinked back" or in cases of acute or chronic lumbago. Rapid and complete relief can be obtained in two days in acute cases if the patient has the fortitude to perform repeatedly the movements that cause most pain. The movement most usually effective is that of repeated dorsiflexion, extension of the back as far as possible. In chronic lumbago such treatment is equally good, but it takes a "few days longer."

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EDITORIALS

THE SESSION IN PHILADELPHIA

THE Nineteenth Annual Clinical Session of the American College of Physicians in Philadelphia will long be recalled in the history of the College not only as having set a new mark in the number of those attending the meeting but also as one of the most interesting of our Annual Sessions in the quality of the program offered

The field of internal medicine is a broad one, but it was fully covered by the Clinic Sessions in the famous medical institutions of this great city and by the carefully chosen papers of the General Sessions. The only difficulty encountered by the visitor lay in making a choice among such a wealth of possibilities, and the only regret was that so many interesting features had to go unvisited for lack of time. There was indeed a question as to whether the feast offered was not too large and varied for even the robust appetite of the College and whether some of the choicest offerings did not go relatively untasted to the natural dissatisfaction of the chefs. If it were so, it was all a part of that gift for endless hospitality which seems characteristic of our Philadelphia colleagues. To all who gave so freely of their talent and of their time for our instruction and our entertainment, the College owes a debt of gratitude.

To those who were unable to attend, the *ANNALS OF INTERNAL MEDICINE* will bring during the coming months the chief papers read at the meeting. In our pages these contributions take their permanent place in the medical literature. The *Annals* can do no more to aid the absentees in retrieving the lost opportunity, but it may and does counsel them to consider the extent of their loss and so lay early plans to attend the Twentieth Annual Clinical Session in Detroit.

THE CERTIFICATION OF SPECIALISTS IN ITS RELATION TO POSTGRADUATE EDUCATION

THE field of prophesy, as all physicians well know, is full of pitfalls, but one cannot contemplate the steady progress of a great movement in our profession without being led to speculate as to its effects upon existing medical customs and institutions. The trend toward certification of all specialists by examining boards under the aegis of the American Medical Association is steadily growing stronger as it gains the adhesion of more and more of the profession. It may well stimulate thought as to its necessary repercussions upon our present medical environment.

In a study of the graduates of the leading medical schools in the United States, Weiskotten found that after a six-year period, from 1920 to 1926,

35 per cent of the total graduates of these schools were partially or completely restricting their practice to a specialty. Perhaps with the increasing crowding in the field of specialism these figures are no longer strictly applicable as indicating the plans of our more recent graduates. Nevertheless it may be assumed that they still roughly indicate the size of the task which is involved in providing really adequate training in the special fields for those who will desire to enter them.

It does of course seem certain that a first effect of elevating the standard of training for specialism will be to decrease the number of those entering upon such training. Such an effect, with an eventual diminution in the number of specialists, may be a gain or a loss. It will be a gain if those who are deterred from specializing are only those who grow faint-hearted at the prospect of further years of serious study, of long hours in the free clinics and on the wards, of tests to be met on the way and of a final examination to be passed. It will be a loss if too many able men are forced to abandon their ambition to specialize only because they lack the money to finance themselves through an expensive postgraduate course. It does not seem unsound to predict that the ultimate true success of the movement for certifying specialists is dependent upon the development of a plan for satisfactory postgraduate education at low cost. In our present system, men of ability who also have sufficient means may obtain satisfactory and systematic postgraduate training either in this country or abroad. A small number of picked men may, through long term residencies and fellowships, obtain valuable but often incomplete training in a specialty in our hospitals and schools. Too many young physicians today, however, are driven to accept as adequate training a year of special internship, a brief period of unsupervised work in the special department of a dispensary, or even a few months in a special course in some graduate school.

It is this last and largest group for which better provision must be made. It seems apparent, since for the most part they must earn a living during the period of training, that they will have to engage in general practice during these years, and that therefore their postgraduate education will have to be confined to a limited period of each day. Moreover, since they cannot pay for this education in money, they will have to find it where the return they can make in professional services will take the place of money.

Those large general dispensary clinics which reorganize themselves so as to provide systematic postgraduate instruction to these young physicians in return for their services will not lack for willing workers, while those which continue to offer nothing more than crowded hours of routine unsupervised work will dwindle away. Funds must be found, it is true, to provide for better equipment, more technical help, and perhaps for some paid instructors in such reorganized clinics. The difficulties in the way are real enough, and not all institutions will be able to solve them. It is not our purpose to propose solutions, but only to indulge in prophecy. Our predictions are

summed up in the statement that there will soon be a rapidly growing demand for adequate postgraduate education acceptable to the various examining boards for the specialties, and that those institutions which reorganize their out-patient clinics to serve as postgraduate schools will be strengthened as a result of this movement, while those who fail to make this adjustment will fall to a lower level

REVIEWS

- (1) *Cho Medica Japanese Medicine* By Y FUJIKAWA, M D Translated from the German by John Ruhrah, M D, with a chapter on the Recent History of Medicine in Japan by Kageyas W Amano, M D, D S C (Med) With 8 illustrations 114 pages Paul B Hoeber, Inc, New York 1934
- (2) *Cho Medica French Medicine* By M LAIGNEL-LAVASTINE and M RAYMOND MOLINERY Translated by E B Krumbhaar, M D With 14 illustrations 187 pages Paul B Hoeber, Inc, New York 1934

This valuable series of primers on the History of Medicine is on its way to become a "collection"—something like the Loeb Edition of the Classics—something that every physician will want always on his shelves and occasionally in his pocket. Ten or twelve of these small attractive volumes have already been published. We have had Egypt and Assyria, Canadian Medicine, Medicine in the British Isles, Italian Medicine, Medicine among the American Indians, with other single volumes on the History of Anatomy, Physiology, Internal Medicine and Nutrition. Now we have Japanese and French Medicine. Many other volumes are in preparation.

The late Dr John Ruhrah has translated from the German the short history of Japanese Medicine by Dr Y Fujikawa, that was prepared by the Japanese Government for the International Exposition of Hygiene at Dresden in 1911. Dr Amano has brought this history up-to-date. Anything that Dr Ruhrah did was well done and this translation of his is clear and concise. The various chapters deal with the periods in medical history that coincide with the main divisions of the history of Japan itself. The Mythical Period ends with about 97 B C—the "old time of the Gods" when "without question the Japanese were on the peninsula of Corea" (p 13), for it was from Corea that the physician Oyu-Ryoda in 552 came to Japan and brought Corean medicine with him. The Nara Period—those of us who have been in Japan will never forget Nara—was a brief one, only some thirty years. Buddhism had been brought to Japan by the Imperial Court and the Buddhist priests occupied much the same place in medicine as did the Christian monks of the Middle Ages. They even established a charity hospital. The Heian Period boasts of the oldest existing medical book of Japan. It is a compendium of extracts from the Chinese Classics, to which the writer adds observations of his own (p 11). It reminds one of similar works in the Byzantine period of Greek Medicine—Oribasius or Paul of Aegina. To anyone who loves Japan, this little History of Medicine is full of names that are fragrant with memories of Japanese beauty. The Kamakura Period, with its revival of Buddhism and the development of Japanese national feeling, brings the reader to the feet of the great silent image of Buddha among the Kamakuran trees. The long Yedo Period, not ending until 1867, takes one to Nikko and the Tokugawa Shoguns—to the great temples with their torii and the long avenues of tall, ancient trees. Here, in the eighteenth century, come Japan's first contacts with the Dutch and other Europeans, and the introduction of European medicine. In the recent years of Japan's medical history, there are famous names known to all of us. Dr Kiyoshi Shiga, who discovered the bacillus of dysentery, Hata, who was associated with Ehrlich and many others.

The book contains a very useful chronological table and a good index of subject and personal names.

Dr E B Krumbhaar, of the University of Pennsylvania and the Editor of the Cho Series, has translated the short history of French Medicine by Drs Laignel-Lavastine and Raymond Molinery. The book falls into the ordinary historical di-

visions, beginning with the period of curative magic and the Gallo-Roman Period. Chapter 3 discusses the real beginnings of French medicine, with an important section on the hospitals of the day, such as the Hotel Dieu of Paris. In the next chapter, which is extremely interesting, we are told how medicine was taught in France a thousand years ago and we learn about the various medical faculties, their powers and important functions. The chapter on the Renaissance is adequate, although comparatively little space is given to Paracelsus or his influence on the French medicine of the day. Chapter 9, dealing with the nineteenth century, is naturally so overloaded with material that it seems somewhat dull—a mere succession of names and discoveries. More interesting is the chapter on Military, Naval and Colonial Medicine. Of course, French medicine no longer holds the important place that it held in former times, such as in the eighteenth and early nineteenth centuries, when all intellectual Europe spoke French.

At the end of the book there is an adequate index and the book is illustrated by fourteen portraits.

J R O

Psychology and Health. By H. BANISTER, M.Sc., Ph.D. 256 pages, 13.5 × 20.5 cm. Macmillan Co., New York. 1935. Price, \$2.50.

The author attempts a survey of psychology in some of its relations to health. "The difficulties which arise at various stages of development, (from infancy onwards) those which occur in physical health and those which follow physical sickness, have been considered, and the diverse kinds of psychological maladjustments which may result have been discussed. The views of the leaders of various schools of psycho-pathology have been outlined, and finally methods of treatment which have stood the test of experience have been sketched," in 245 small pages.

The book is very readable, if one wishes a superficial presentation of current psychological views. Hypnosis, little used, at least in this country, seems overstressed. The followers of the schools indicated (Freud, Jung and Adler) would probably take issue with this interpretation of their views. The genetic-dynamic formulation so widely followed in America is not mentioned. The chapters on treatment are well done, though even here the tendency to reduce everything to *a*, *b*, *c*, but rarely *d* rouses in us the profound wish—long since lost—that mental disease were this simple and easy to understand and treat.

H M M

Food for the Diabetic. By MARY P. HUBBARDSON. viii + 110 pages, 13 × 19 cm. Macmillan Company, New York. 1934. Price, \$1.50.

It is evident that this book has filled a demand because it is now in its third edition. The title is not quite accurate, since almost half the book is devoted to an exposition of the nature of diabetes and its medical treatment, to urinary examination, the administration of insulin and the prevention of the disease. The discussion of food measurement, the calculation of the food prescription, and the construction of meals are all clearly and logically developed. Two hundred grams of milk are considered an adequate adult intake (page 16), cereals and breads are to be selected from the "whole grain" variety. The food tables are well grouped, in nine small pages. They may be used both for weighed and measured diets. There is a chapter of recipes. The merit of this book lies in its simplicity and in its wise selection of essentials.

G A H

Sex-Hygiene What to Teach and How to Teach It By ALFRED WORCESTER, M D
134 pages, 16 X 24 cm Charles C Thomas, Baltimore 1934 Price, \$2 50

We have often wondered why it seems to be impossible to adopt the same objective, matter-of-fact attitude toward sex-hygiene and related topics that we show toward other forms of hygiene and medicine in general. Authors apparently must cloud the issue with moral and religious considerations, or titillate their readers with all the lurid details. This book is of the former type. It contains twelve pleasant, semi-religious essays which have been delivered over the course of the last thirty-five years to a variety of lay and professional groups of men and women. In Dr Worcester's hands this may work well, but we are perfectly sure that if we responded to a question as to how far "petting parties" may go and what we thought of them by talking of our responsibility "to our Creator for the safeguarding of the human life life-stream", by telling the boy he should treat the girl as he would wish his sister to be treated, by telling the girl she must win his respect and admiration and be true to his trust, and by telling both that "Restraint for each other's sake is in itself soul-satisfying and also a far more powerful motive than mere self-protection", we would meet an incredulously lifted eye brow and politely restrained mirth.

Dr Worcester's fundamental attitude is sound, but his exposition is not helpful in dealing with average young people, who do not seem to stop to think about their Creator very often or to make Him part of their daily lives.

H M M

Diseases of Children By SIR A E GARROD, FREDERICK E BATTEN, HUGH THURSFIELD, and DONALD PATERSON 1152 pages, 17 X 24 5 cm William Wood and Company, Baltimore 1934 Price, \$10 00

This is a new and completely revised edition of one of the leading English textbooks on pediatrics. The last edition was in 1929. The present volume shows many changes and additions.

The addition of an article on Heredity at the beginning of the book is a happy thought. The article on the teeth with stress laid on their maldevelopments and on their relation to general health is also a valuable feature. There are excellent discussions by Cameron on functional diseases of the nervous system and by Bray on allergy. The article by Sheldon on "Rheumatism" is admirably handled. In general the various contributors have maintained a high standard.

The American physician will not derive much value from certain statements on therapy because of unfamiliarity with the trade names of the Infant Formulary. He will be surprised also to learn that in pneumonia "the application of leeches over the hepatic area followed by hot fomentation to encourage further bleeding, will usually produce relief for the embarrassed right heart" (Page 432). On page 47 viosterol dosage is stated as "a few drops given three times daily".

The rarer diseases are included and one finds space allotted to Von Gierke's disease, Progeria Alkaptonuria, etc. There is of necessity a certain amount of overlapping. Ample reference lists are handily placed at the end of each article. The illustrations are excellent and well selected, there are two valuable colored plates. The book as a whole is an excellent general pediatric text.

E B

COLLEGE NEWS NOTES

At the Annual Business Meeting of the College held at Philadelphia, May 2, 1935, the following elections took place

A Elective Officers

President-Elect

First Vice-President

Second Vice-President

Third Vice-President

Dr Ernest B Bradley, Lexington Ky

Dr Arthur R Elliott, Chicago, Ill

Dr David P Barr, St Louis, Mo

Dr Egerton L Crispin, Los Angeles, Calif

B Regents, term expiring 1938

Dr Jonathan C Meakins

Dr James H Means

Dr James B Herrick

Dr Charles G Jennings

Dr James E Paullin

Montreal, Que

Boston, Mass

Chicago, Ill

Detroit, Mich

Atlanta, Ga

C Governors, term expiring 1938

Dr James F Churchill

Dr Gerald B Webb

Dr Henry F Stoll

Dr Wallace M Yater

Dr Ernest E Laubaugh

Dr Samuel E Munson

Dr Robert M Moore

Dr Thomas Tallman Holt

Dr William B Breed

Dr Adolph Sachs

Dr Allen A Jones

Dr Leander A Riely

Dr Edward J G Beardsley

Dr E Bosworth McCready

Dr J Owsley Manier

Dr Louis E Viko

Dr Jabez H Elliott

Dr William M James

Southern California—San Diego

Colorado—Colorado Springs

Connecticut—Hartford

District of Columbia—Washington

Idaho—Boise

Southern Illinois—Springfield

Indiana—Indianapolis

Kansas—Wichita

Massachusetts—Boston

Nebraska—Omaha

Western New York—Buffalo

Oklahoma—Oklahoma City

Eastern Pennsylvania—Philadelphia

Western Pennsylvania—Pittsburgh

Tennessee—Nashville

Utah—Salt Lake City

Ontario—Toronto, Canada

Panama and the Canal Zone

Term Expiring 1937

Dr C W Dowden

Dr C G Giddings

Dr Ramon M Suarez

Kentucky—Louisville

Georgia—Atlanta

Puerto Rico—San Juan

At a meeting of the Board of Regents at Philadelphia, April 28, 1935, the following elections to Fellowship and Associateship were made

Elected to Fellowship

April 28 1935

Alexander, Archibald Addison

Alexander, Harry L

Baldwin, Louis B

Ball, Ralph G

Belk, William Parks

Bell, J Kenner

Black, James Harvey

Boman, Paul Gerhard

Oakland, Calif

St Louis, Mo

Tucson, Ariz

Manhattan, Kan

Ardmore, Pa

Detroit, Mich

Dallas, Texas

Duluth, Minn

Brown, Lewis Woodbridge
 Burlingame, Clarence Charles
 Cardle, Archibald Evans
 Carns, Marie Louise
 Chappell, Sidney L
 Chrisman, William Walter
 Colomb, Henry O
 Compton, Marion Lee
 Condry, Raphael Joseph
 Corr, Wm Philip
 Cottrell, James Ewing
 Cozby, Harold Otis
 Cronwell, Bernhard J, Jr
 Crowe, Aldrich Clements
 Deegan, John Kenneth
 Denison, Robert
 Denno, Willard Joseph
 Dieuaide, Francis Raymond
 Dillon, Edward Saunders
 Dollard, Henry Louis
 Duhigg, Thomas F
 Durgin, Lawrence Newton
 Fenby, John S
 Fineman, Abraham Harold
 Flinn, Robert Stanley
 Frazier, Chester North
 Fregeau, Aime Napoleon
 Gardner, Walter P
 Goldstein, Eli
 Gordon, Burgess Lee
 Gordon, Douglas Meharg
 Graham, William Randolph
 Griffin, Mark Alexander
 Griffith, George Cupp
 Harvey, Andrew
 Helwig, Ferdinand C
 Higgins, John Mark
 Hill, Walter Herbert
 Hines, Laurence Edward
 Horger, Eugene Lerov
 Hovenden, Ontie
 Hunter, Melville Wallace
 Hutton, James H
 Ilsley, Morrill Leonard
 LaMont, Charles A
 Lawson, Herman Albert
 Leak, Roy L
 Levin, Charles Morris
 Levitas, George Max
 Lewis, Paul John
 Margolis, Harry Maurice
 Markel, Albert G
 McEnerney, Charles Harold
 McNeill, Philip M

Newark, N J
 Hartford, Conn
 Minneapolis, Minn
 Madison, Wis
 M C, U S Army
 Macon, Ga
 Sykesville, Md
 Lexington, Ky
 Elkins, W Va
 Riverside, Calif
 Philadelphia, Pa
 M C, U S Navy
 Austin, Minn
 Ocean City, N J
 Albany, N Y
 Harrisburg, Pa
 New York, N Y
 Peiping, China
 Philadelphia, Pa
 Washington, D C
 M C, U S Navy
 Amherst, Mass
 Baltimore, Md
 New York, N Y
 Phoenix, Ariz
 Peiping, China
 San Francisco, Calif
 Hastings, Minn
 New York, N Y
 Philadelphia, Pa
 Ponca City, Okla
 Richmond, Va
 Biltmore, N C
 Philadelphia, Pa
 New York, N Y
 Kansas City, Kan
 Sayre, Pa
 San Antonio, Texas
 Chicago, Ill
 Columbia, S C
 McGill, Nevada
 Monroe, La
 Chicago, Ill
 Claremont, Calif
 Canton, Ohio
 Providence, R I
 Middletown, Conn
 Richmond Hill, N Y
 Westwood, N J
 Yakima, Wash
 Pittsburgh, Pa
 Paterson, N J
 Washington, D C
 Oklahoma City, Okla

Mitchell, Louis Albert
 Morris, Sarah I
 Nakada, James Robert
 Osgood, Carroll Wilcox
 Randolph, Howell Sheppard
 Redwood, Frank Harrell
 Rose, Edwin Jehu
 Schiltz, Frances Helen
 Scholz, Samuel B
 Scott, James Ralph
 Sexton, Daniel Leritz
 Sheldon, Lawrence Burton
 Sinnock, Hildegard Catherine G
 Sprague, Charles Harry
 Squires, Willard Haywood
 Swalm, William A
 Whalen, Neil James
 Willman, Frank Louis
 Wyckoff, John
 Ylvisaker, Lauritz S

Newark, Ohio
 Philadelphia, Pa
 St Louis, Mo
 Wauwatosa, Wis
 Phoenix, Ariz
 Norfolk Va
 Washington, D C
 Wichita, Kan
 Philadelphia, Pa
 New York, N Y
 St Louis Mo
 Dallas, Texas
 Quincy, Ill
 Bridgeport, Conn
 New York, N Y
 Philadelphia, Pa
 Detroit, Mich
 Washington, D C
 New York, N Y
 Newark, N J

Elected to Associateship

April 28, 1935

Algie, William H
 Allen, Kenneth Dayton Allison
 Bach, Theodore Franklin
 Bailey, Fuller B
 Baird, David W
 Baird, John Adams
 Barber, Thomas Maxfield
 Bauer, Louis Hopewell
 Bell, George Erick
 Bennett, Clarence Rhodes
 Bixby, Edward Welles
 Black, Everett O
 Bonner-Miller, Lila Morse
 Brennan, Joseph Patrick
 Brines, Osborne Allen
 Brust, Raymond W
 Buchanan, J Arthur
 Buck, Burdette Jay
 Cahall, Walter Lawrence
 Cake, Charles Powell
 Carlson, Glenn DeVere
 Catchings, Charles Evans
 Chavarria, Antonio Pena
 Ching, Richard Edward
 Collman, Xavier Kuehn
 Collins, Leon Howard, Jr
 Comroe, Bernard Isaac
 Connelly, Richard Campbell
 Conwell, Daniel Vincent

Clay Center, Kan
 Denver, Colo
 Philadelphia, Pa
 Salt Lake City, Utah
 Portland, Ore
 Dayton, Ohio
 Charleston, W Va
 Hempstead, N Y
 Wilson, N C
 Eufaula, Ala
 Wilkes-Barre, Pa
 Binghamton, N Y
 Raleigh, N C
 Pendleton, Ore
 Detroit, Mich
 Philadelphia, Pa
 Brooklyn, N Y
 Hartford, Conn
 Philadelphia, Pa
 Washington, D C
 Dallas, Tex
 Woodville, Miss
 San Jose, Costa Rica
 Memphis, Tenn
 Wilkes-Barre, Pa
 Philadelphia, Pa
 Philadelphia, Pa
 Detroit, Mich
 Halstead, Kan

Corrigan, George Francis
 Corrigan, John Cosgrove
 Covner, Albert Henry
 Crane, Langdon Teachout
 Crellin, Jacob Antrim
 Danglade, James H
 Daniels, Harry Anthony
 Decherd, George Michael, Jr
 Deweese, Everett R
 DuBois, Earl Danford
 Durkin, Harry Anthony
 Egloff, William Chauncey
 Fetter, Ferdinand
 Flowers, Hiland L
 Fortney, Arthur Conwell
 Foster, Robert Francis
 Foster, Stuart Oliver
 Fox, Everett Clarence
 Gallison, Davis Thayer
 Ganim, Joseph Nicholas
 Gillick, David W
 Gilman, Ralph Lawrence
 Golan, Harry G
 Goldburgh, Harold L
 Gordon, Abraham S
 Gordon, Harold
 Griffith, Reynold Stephen
 Hailey, David Walter
 Hawkes, Richard Sylvester
 Hilton, John Palmer
 Hindman, Samuel
 Hitzrot, Lewis Haler
 Hoedemaker, Edward David
 Hoffman, Kelse Monjar
 Hood, Frederick Redding
 Horan, Thomas M
 Horn, Benjamin
 Hufford, Clarence Elton
 Hunter, Charles Teague
 Ianne, Charles L
 Jantzen, George Howard
 Kennedy, Allan Souter
 Kennedy, Paul Augustin
 Keyes, Baldwin Longstreth
 Knight, Albert P
 Knighton, James Edward, Jr
 Kullman, Harold John
 Landay, Louis Harold
 Lang, Samuel John
 LeBauer, Sidney F
 Leonard, Noble Day
 Lincoln, Cicero Lee

Wichita, Kan
 Boston, Mass
 Lynn, Mass
 Detroit, Mich
 Lansdowne, Pa
 Kansas City, Mo
 Oklahoma City, Okla
 Galveston, Tex
 Kansas City, Mo
 Portland, Ore
 Peoria, Illinois
 Mason City, Iowa
 Philadelphia, Pa
 New York, N Y
 Fargo, N D
 Rochester, Minn
 Washington, D C
 Dallas, Tex
 Boston, Mass
 Cincinnati, Ohio
 Shawnee, Okla
 Storrs, Conn
 Richmond Hill, N Y
 Philadelphia, Pa
 Brooklyn, N Y
 Louisville, Ky
 Philadelphia, Pa
 Nashville, Tenn
 Portland, Maine
 Denver, Colo
 Cleveland, Ohio
 Philadelphia, Pa
 Seattle, Wash
 Franklin, Pa
 Oklahoma City, Okla
 Detroit, Mich
 Bridgeport, Conn
 Toledo, Ohio
 Newtown, Pa
 San Jose, Calif
 Queens Village, N Y
 Hamilton, Ont, Canada
 Englewood, N J
 Philadelphia, Pa
 Sayre, Pa
 Shreveport, La
 Detroit, Mich
 Aliquippa, Pa
 Evanston, Illinois
 Greensboro, N C
 North Chicago, Illinois
 Denver, Colo

Lockie, L Maxwell
 Maloney, Edward S
 Margason, Merl L
 Marlow, Arthur Ashlev
 Marr, Norval Mason
 Martin, Maynard Waite
 Masten, Alfred Roe
 McClenahan, William Urie
 McGee, Lemuel C
 McGuire, Johnson
 McInerney, Michael J
 McKay, Donald Robert
 Miller, James Roscoe
 Miller, Merle Middour
 Miller, William Lindsay
 Moench, L Mary
 Molitch, Matthew
 Monte, Louis Anthony
 Moore, Norman Slavson
 Moser, Rollin Henry
 Mudgett, William Chase
 Myers, Walter Kendall
 Nye, Robert Bruce
 Osterman, Arthur Lee
 Perkin, Frank S
 Pitts, Thomas Antley
 Plotz, Milton
 Plunkett, John Elmer
 Polansky, John Basil
 Potts, William Henry, Jr
 Price, Alvin Edwin
 Pruitt, Lee Tinkle
 Reddick, Walter Grady
 Reed, Ivor Ellsworth
 Reichert, Philip
 Rice, Raymond Maine
 Robertson, Harold F
 Rosenfeld, Joseph
 Rothenberg, Robert Charles
 Rubnitz, Abraham S
 Sanders, Charles B
 Schmitz, Henry L
 Schneck, Robert J
 Schoch, Arthur Gerhard
 Scott, Ernest G
 Selling, Lowell Sinn
 Sewell, Harry Dickey
 Shapiro, Matthew
 Simon, Frank A
 Smith, Euclid Monroe
 Smith, Lauren Howe
 Smith, Percy King

Buffalo, N Y
 Omaha, Nebr
 Portland, Ore
 Peiping, China
 St Petersburg, Fla
 Cleveland, Ohio
 Wheat Ridge, Colo
 Philadelphia, Pa
 Elkins, W Va
 Cincinnati, Ohio
 Washington, D C
 Buffalo, N Y
 Chicago, Illinois
 Philadelphia, Pa
 Gadsden, Ala
 New York, N Y
 Jamesburg, N J
 New Orleans, La
 Ithaca, N Y
 Indianapolis, Ind
 Southern Pines, N C
 Washington, D C
 Philadelphia, Pa
 Wheeling, W Va
 Detroit, Mich
 Columbia, S C
 Brooklyn, N Y
 Rochester, Minn
 Glenside, Pa
 Dallas, Texas
 Detroit, Mich
 Beaumont, Texas
 Dallas, Texas
 Detroit, Mich
 New York, N Y
 Council Bluffs, Iowa
 Philadelphia, Pa
 Youngstown, Ohio
 Cincinnati, Ohio
 Omaha, Nebr
 Dallas, Texas
 Chicago, Illinois
 Detroit, Mich
 Dallas, Texas
 Lynchburg, Va
 Detroit, Mich
 Huron, S D
 New York, N Y
 Louisville, Ky
 Hot Springs National Park, Ark
 Philadelphia, Pa
 Wichita Falls, Texas

Smith, Richard Mays
 Southcombe, Robert Henry
 Speight, Harold E
 Sprenkel, Vaughan Le Roy
 Stalker, Hugh
 Stiles, Merritt Henry
 Tolleson, Henry Madison
 Underwood, George R
 Walker, Thomas Tipton
 Warvel, John Henry
 Wells, Robert Lomax
 Whiting, Walter Belknap
 Willhelmy, Ellis W
 Wilson, George Campbell
 Wilson, Robert, Jr
 Wolfson, Mast
 Wood, Francis Clark
 Wood, J K Williams

Dallas, Texas
 Medical Lake, Wash
 Middletown, Conn
 Allentown, Pa
 Grosse Pointe, Mich
 Philadelphia, Pa
 Eastman, Ga
 Lincoln, Nebr
 Watertown, N Y
 Indianapolis, Ind
 Washington, D C
 Wichita Falls, Texas
 Kansas City, Mo
 Wallingford, Conn
 Charleston, S C
 Monterey, Calif
 Philadelphia, Pa
 Willow Grove, Pa

OBITUARY

WILLIAM SESSIONS HANNAH

Dr William Sessions Hannah of Montgomery, Alabama, died of a streptococcus infection in Buffalo, New York, on March 22, 1935, after an illness of only a few days

Dr Hannah became an Associate of the College of Physicians in 1932 and was to be presented for Fellowship this year

He was born in Pensacola, Florida, but had lived in Montgomery, Alabama, for many years His academic education was obtained at the University of Alabama and Tulane University and he graduated in medicine at Johns Hopkins University in 1924 For four years he was an intern in the Union Memorial Hospital, finishing his internship in 1928, after which he located in his home town of Montgomery for the practice of his profession

Dr Hannah was a young man of splendid attainments He was well trained medically, was a man of culture, and a gentleman of the highest type He was rapidly making his mark in his profession and was destined to reach great heights He had the respect and confidence of the community not only for his medical skill, but for his honor and integrity as a man His death at so young an age is greatly to be deplored

FRED WILKERSON, M D , F A C P ,
 Governor for Alabama

DETROIT SELECTED FOR 1936 ANNUAL SESSION

At a meeting of the Board of Regents held May 3, 1935, on the closing day of the Philadelphia Annual Session, the invitation from Detroit for the 1936 Annual Session of the College was accepted by the Board of Regents Dr James Alex Miller, President, appointed Dr Charles G Jennings of Detroit as General Chairman of the Session Announcement will later be made of the hotel headquarters and the place of meetings

The University of Michigan Medical School, located at Ann Arbor, will cooperate in the program for 1936

The College last met in Detroit during 1926, at which time the American Congress on Internal Medicine was merged with the College, members of that Society becoming Associates of the College

THE AMERICAN COLLEGE OF PHYSICIANS

EXECUTIVE SECRETARY'S REPORT ON OPERATION
1934

The auditor's report of his examination of the accounts of the College is hereto attached The statements disclose a further improvement over the preceding two years, as shown by the following

| | |
|--------------|--------------|
| 1932 Surplus | \$ 10,598 08 |
| 1933 " | 5,801 06 |
| 1934 " | 16,160 07 |

The 1934 surplus was distributed as follows

| | |
|----------------|--------------|
| Endowment Fund | \$ 1,710 00 |
| General Fund | 14,450 07 |
| | <hr/> |
| | \$ 16,160 07 |

The total principal of the two Funds on December 31, 1934 was

| | |
|----------------|--------------|
| Endowment Fund | \$ 55,720 00 |
| General Fund | 84 427 10 |
| | <hr/> |
| | \$140,147 10 |

The larger surplus may be attributed to somewhat improved conditions among physicians, to additions to the membership, increased circulation of the ANNALS OF INTERNAL MEDICINE and a gradual transition from the smaller number of elections to Fellowship because of the "Associate first" rule which became operative in 1931 The number eligible for Fellowship was small during 1931, 1932 and 1933, but beginning 1934 the number began to increase, showing an appreciable effect on the income from initiation fees The cost of printing the ANNALS OF INTERNAL MEDICINE was materially reduced during 1934 due to a change in printers

Liquidating dividends were received from two of the former College depositories, now in the hands of receivers, in the total amount of \$2,728 15, leaving a balance in such banks of \$9,171 85

A condensed comparison of income and expenditures for 1933 and 1934 appears on the following page

The Executive Office has been conducted conservatively, with expenditures held to a minimum for effective operation

Respectfully submitted

(Signed) E R LOVELAND,
Executive Secretary

April 28, 1935

A CONDENSED COMPARISON OF INCOME AND EXPENDITURES FOR 1933 AND 1934

| | <i>General Fund</i> | |
|---------------------------|---------------------|-------------|
| <i>Income</i> | 1933 | 1934 |
| Annual Dues | \$20,069 80 | \$20,875 35 |
| Initiation Fees | 2 856 68 | 6,142 32 |
| Interest on Investments | 1,977 32 | 3,117 89 |
| Interest on Bank Balances | 243 28 | 22 50 |

| | | |
|--|--------------------|--------------------|
| Profit on Sale of Securities | 2 96 | 1,178 39 |
| Subscriptions, ANNALS OF INTERNAL MEDICINE | 17,785 81 | 19,528 05 |
| Advertising, ANNALS OF INTERNAL MEDICINE | 4,540 20 | 4,455 28 |
| Exhibits, Annual Clinical Session | 4,192 21 | 6,124 85 |
| Guest Fees, Annual Clinical Session | 374 50 | 448 00 |
| Miscellaneous Income | 266 15 | 67 38 |
| | <u>\$52,308 91</u> | <u>\$61,960 01</u> |
| <i>Expenditures</i> | | |
| Annual Clinical Session | \$10,527 26 | \$11,646 40 |
| ANNALS OF INTERNAL MEDICINE | 19,540 36 | 19,216 05 |
| Executive Secretary's Office | 16,419 02 | 15,647 70 |
| Miscellaneous | 556 21 | 624 79 |
| | <u>\$47,042 85</u> | <u>\$47,134 94</u> |
| <i>Endowment Fund</i> | | |
| <i>Income</i> | | |
| Interest on Investments | \$ 2,385 86 | \$ 2,311 63 |
| Life Membership Fees | 635 00 | 1,710 00 |
| | <u>\$ 3,020 86</u> | <u>\$ 4,021 63</u> |
| <i>Expenditures</i> | | |
| John Phillips' Memorial Award | \$ 1,025 20 | |
| Research Fellowship | | \$ 450 00 |

H I MACLEAN

Penarth Avenue and State Road

Bywood, Pa

February 25, 1935

To the Board of Regents
American College of Physicians, Inc
Philadelphia, Pa

*Mr E R Loveland, Executive Secretary**Dear Sirs*

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC

for the year ended December 31, 1934, and the accompanying statements, including the Balance Sheet at December 31, 1934, the analyses of the General Fund and the Endowment Fund, and the Statement of Operations for the year ended December 31, 1934, are in accordance with books of account and in my opinion set forth correctly the financial position at December 31, 1934, and the results of operations for the calendar year ended December 31, 1934, subject to the following comments

Cash The cash was properly accounted for The following is a statement of the cash in the various depositories

| | |
|---|--------------------|
| Girard Trust Company, Philadelphia | \$37,020 57 |
| Provident Trust Company, Philadelphia | 17,239 44 |
| Royal Bank of Canada, Montreal | 3,933 82 |
| Philadelphia Saving Fund Society (Time Deposit) | 2,511 25 |
| Western Saving Fund Society (Time Deposit) | 2,511 25 |
| | <u>\$63,216 33</u> |

The amount of cash in closed banks at January 1, 1934, was \$11,900 00, during the year liquidating dividends amounting to \$2,728 15 were received, which reduced the amount to \$9,171 85, as shown by the following schedule

| | Balance Jan 1, 1934 | Liquidating Dividends | Balance Dec 31, 1934 |
|------------------------------------|------------------------|--------------------------|-------------------------|
| Bank of Pittsburgh, Pittsburgh | \$ 5,847 87 | \$2,436 61 | \$3,411 26 |
| Exchange National Bank, Pittsburgh | 2,040 74 | 291 54 | 1,749 20 |
| Highland National Bank, Pittsburgh | 4,011 39 | | 4,011 39 |
| | <u>\$11,900 00</u> | <u>\$2,728 15</u> | <u>\$9,171 85</u> |

Accounts Receivable The accounts receivable were examined and found to be less than one year old and appear to be good and collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments The securities were properly accounted for by direct correspondence with the Girard Trust Company of Philadelphia, and the income for the year therefrom was verified. It was noted that the recommendation contained in the audit report that the securities be allocated to specific funds had not been carried out during the year ended December 31, 1934. However, it was further noted that the Board of Regents had taken action at the meeting of December 16, 1934, indicating that such allocation should be made. It is my understanding, after consultation with the Executive Secretary, Mr. E. R. Loveland, that the securities would be allocated to specific funds as of January 1, 1935. The net gain on the securities sold during this year has been credited to operations. The income from investments was distributed to the General Fund and to the Endowment Fund on the basis of the average yield for the period of 4.28 per cent. At December 31, 1934, the following security was in default:

| | Interest in Default |
|--|---------------------|
| \$2,000 City of Detroit, Mich. Lighting, 4 1/4, 1944 | May, 1933 \$42 50 |
| | Nov., 1933 14 17 * |
| | May, 1934 14 17 * |
| | Nov., 1934 42 50 |

General The increase in the amount of the Endowment Fund and the General Fund during the year 1934 is as follows:

| | Balance Dec 31 1933 | Balance Dec 31, 1934 | Net Increase |
|----------------|------------------------|-------------------------|--------------------|
| Endowment Fund | \$ 54,010 00 | \$ 55,720 00 | \$ 1,710 00 |
| General Fund | 69,977 03 | 84,427 10 | 14,450 07 |
| | <u>\$123,987 03</u> | <u>\$140,147 10</u> | <u>\$16,160 07</u> |

The accrued and deferred items have been recorded properly and were verified, the footings and extensions of the inventory were verified, the charges to the furniture and equipment accounts were proper and the allowance for depreciation appears to be adequate and all ascertainable liabilities have been included in the Balance Sheet. All recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank and all disbursements as indicated by the vouchers, cancelled checks and bank statements were properly recorded in the books of account.

Very truly yours,

(Signed) H. I. MACLEAN,
Certified Public Accountant

* Part payments of the interest due on November 15, 1933, and May 15, 1934, were received amounting to \$28.33 on each due date or a total of \$56.66.

AMERICAN COLLEGE OF PHYSICIANS, INC

BALANCE SHEET, DECEMBER 31, 1934

Assets

| | | | |
|---|-------------|-------------|---------------------|
| Cash | | | |
| In Banks and on Hand | | \$63,416 33 | |
| In Closed Banks | | | |
| Bank of Pittsburgh | \$3,411 26 | | |
| Exchange National Bank, Pittsburgh | 1,749 20 | | |
| Highland National Bank, Pittsburgh | 4,011 39 | 9,171 85 | \$ 72,588 18 |
| Accounts Receivable | | | 303 35 |
| Investments at cost, as annexed | | | 64,986 06 |
| Accrued Interest on Investments | | | 726 77 |
| Inventory of Keys, Pledges and Frames, at cost | | | 332 69 |
| Deferred Expenses, 19th Annual Clinical Session | | | 2,146 49 |
| Furniture and Equipment, at cost | \$ 4,019 90 | | |
| Less, Allowance for Depreciation | 2,348 59 | | 1,671 31 |
| | | | <u>\$142,754 85</u> |

Liabilities

| | | | |
|--|-------------|--------|----------|
| Deferred Income | | | |
| Advance Collections for Exhibits, Nineteenth Annual Clinical Session | \$ 2,310 46 | | |
| Advance Subscriptions for Volume IX, ANNALS OF INTERNAL MEDICINE | | 297 29 | 2,607 75 |

Funds

| | | | |
|----------------------------|-------------|------------|---------------------|
| Endowment Fund, as annexed | \$55,720 00 | | |
| General Fund, as annexed | 84,427 10 | 140,147 10 | |
| | | | <u>\$142,754 85</u> |

General Fund

For the Year Ended December 31, 1934

| | |
|---|--------------------|
| Balance, January 1, 1934 | \$69 977 03 |
| Less | |
| Transfer to Endowment Fund of the Initiation Fees of six new Life Members | 375 00 |
| | <u>\$69,602 03</u> |

Summary of Operations for the year ended December 31, 1934

Income

| | | |
|--|-------------|-------------|
| Annual Dues | \$20,875 35 | |
| Subscriptions, ANNALS OF INTERNAL MEDICINE | 19,528 05 | |
| Advertising, ANNALS OF INTERNAL MEDICINE | 4,455 28 | |
| Initiation Fees | 6,142 32 | |
| Income from Invested Funds | 3,117 89 | |
| Profit on Sale of Securities | 1,178 39 | |
| Exhibits, 18th Annual Clinical Session | 6,124 85 | |
| Guest Fees, 18th Annual Clinical Session | 448 00 | |
| Other Income | 89 88 | \$61,960 01 |

Expenses

| | |
|------------------------------------|-------------|
| Salaries | \$17,415 60 |
| Postage, Telephone, Telegraph, etc | 2,571 87 |
| Office Supplies and Stationery | 1,016 48 |
| Printing | 14,269 52 |
| Rent and Maintenance | 2,785 73 |
| Traveling Expenses | 5,331 04 |

| | |
|------------------------------|--------------------|
| Other Expenses | |
| 18th Annual Clinical Session | 2,187 77 |
| ANNALS OF INTERNAL MEDICINE | 349 66 |
| Executive Secretary's Office | 602 48 |
| Miscellaneous | 604 79 |
| | <u>\$47,134 94</u> |

Net Income for the year ended December 31, 1934 14,825 07

Balance, December 31, 1934 \$84,427 10

Endowment Fund

For the Year Ended December 31, 1934

| | |
|---|--------------------|
| Principal Account | |
| Balance, January 1, 1934 | \$54,010 00 |
| Add | |
| Life Membership Fees received during 1934 | 1,335 00 |
| Transfer of Initiation Fees of six new Life Members from General Fund | 375 00 |
| | <u>\$55,720 00</u> |
| Total, December 31, 1934 | |

| | |
|---|--------------------|
| Income Account | |
| Income from Securities (Endowment Fund only) | 2,311 63 |
| Less, | |
| Research Fellowship | 450 00 |
| | <u>\$ 1,861 63</u> |
| Balance, Transferred to Operations for the Period | |

STATEMENT OF OPERATIONS

For the Year Ended December 31, 1934

| | |
|--|--------------------|
| <i>General Income</i> | |
| Annual Dues | \$20,875 35 |
| Initiation Fees | 6,142 32 |
| Income from Endowment Fund (Net after deducting Research Fellowship stipend) | 1,861 63 |
| Income from General Investments | 1 256 26 |
| Profit on Sales of Securities (Net) | 1,178 39 |
| Profit from Sale of Keys, Pledges and Frames | 61 88 |
| Interest on Bank Balances | 22 50 |
| Sales of 1933 Directory | 5 50 |
| | <u>\$31,403 83</u> |

Eighteenth Annual Clinical Session

| | |
|----------------|--------------------|
| Income | |
| Exhibits (Net) | \$ 6,124 85 |
| Guest Fees | 448 00 |
| | <u>\$ 6,572 85</u> |

| | |
|--|--------------------|
| Expenses | |
| Salaries | 3,898 35 |
| Communications (Postage, Telephone, Etc) | 364 99 |
| Office Supplies and Stationery | 68 12 |
| Printing | 1,266 88 |
| Traveling Expenses | 3,860 29 |
| Miscellaneous | |
| Advertising | \$ 159 65 |
| Badges | 231 86 |
| Convocation and President's Reception | 246 96 |
| Equipment Rental (Lanterns etc) | 215 00 |
| Ladies Committee | 165 37 |
| Publicity and Reporting | 454 02 |
| Smoker | 520 09 |
| Loss on Banquet (Net) | 51 07 |
| Other Miscellaneous Items | 143 75 |
| | <u>\$ 2,187 77</u> |
| | <u>\$11,646 40</u> |

Net Expenses of Clinical Session \$ 5,073 55

ANNALS OF INTERNAL MEDICINE

Income

Subscriptions

| | | | |
|----------|----|-----------|-------------|
| Volume I | \$ | 6 90 | |
| " II | | 7 90 | |
| " III | | 7 30 | |
| " IV | | 9 30 | |
| " V | | 7 30 | |
| " VI | | 50 37 | |
| " VII | | 1,100 78 | |
| VIII | | 18,338 20 | \$19,528 05 |

Advertising (Net)

| | | |
|------------|----------|-----------------|
| Volume VII | 2,494 90 | |
| " VIII | 1,960 38 | \$ 4,455 28 |
| | | <hr/> 23,983 33 |

Expenses

| | | |
|--|-----------|-------------|
| Salaries | 5 137 26 | |
| Communications (Postage, Telephone etc) | 842 23 | |
| Office Supplies and Stationery | 494 47 | |
| Printing | 12 392 43 | |
| Miscellaneous | 134 11 | |
| Allowances, Adjustments and Purchases | 215 55 | \$19,216 05 |

Net Profit on ANNALS OF INTERNAL MEDICINE

4 767 28

Total Income

\$36,171 11

Executive Secretary's Office

Expenses

| | | |
|--|-------------|-----------|
| Salaries | \$ 8,379 99 | |
| Communications (Postage, Telephone etc) | 1,364 65 | |
| Office Supplies and Stationery | 453 89 | |
| Printing | 610 21 | |
| Rent and Maintenance | 2 785 73 | |
| Traveling Expenses | 1,470 75 | |
| Fee to Custodian of Securities | 115 79 | |
| Loss on Foreign Exchange | 7 33 | |
| Tax on Checks | 13 83 | |
| Loss on Sale of Equipment | 15 20 | |
| Miscellaneous | 430 33 | 15 647 70 |

ANNALS OF INTERNAL MEDICINE

| | | |
|---|--------|-----------|
| Distributed Free to Life Members | 216 00 | |
| Depreciation on Furniture and Equipment | 408 79 | 21,346 04 |

Net Income for the Year Ended December 31, 1934

\$14 825 07

INVESTMENTS

December 31, 1934

| Par Value | Bonds | Cost |
|-----------|---|-------------|
| \$ 2,000 | Canadian National (West Indies) SS Co Ltd 5s, 1955 | \$ 2,040 00 |
| 2,000 | City and County of San Francisco, Calif, Fire Protection, 5s 1941 | 2,137 12 |
| 2,000 | City of Detroit, Mich, Lighting, 4¼s, 1944 | 2,010 40 |
| 2,000 | City of Detroit, Mich, Street Railway, 4¼s, 1949 | 2,025 26 |
| 2,000 | City of Houston Tex, School District, 4¼s, 1942 | 2,077 50 |
| 1,000 | City of Montreal Canada, 5s, 1956 | 1,071 30 |
| 2,000 | City of Toronto, Canada, Local Improvement, Debenture, 5s, 1936 | 2,020 00 |
| 5,000 | Commonwealth Edison Co, First, Series "F," 4s, 1981 | 4,744 35 |
| 5,000 | Government of the Dominion of Canada, 4s, 1960 | 4,662 50 |

| | | |
|-----------------|--|--------------------|
| 5,000 | New York and West Chester, Lighting, General Mortgage, 4s, 2004 | 5,044 35 |
| 5,000 | Pennsylvania Railroad, General Mortgage, Series "E," 4 $\frac{1}{4}$ s, 1984 | 5,013 10 |
| 2,000 | Port of New York Authority, Interstate Bridge, Series "B," 4 $\frac{1}{2}$ s, 1952 | 2,042 20 |
| 2,000 | Port of New York Authority, Interstate Tunnel, Series "E," 4 $\frac{1}{4}$ s, 1958 | 2,065 40 |
| 1,000 | Province of Ontario, Canada, Debenture, 5s, 1942 | 1,052.26 |
| 2,000 | Province of Ontario, Canada, 4 $\frac{1}{2}$ s, 1942 | 2,015 00 |
| 3,000 | U S Fourth Liberty Loan, 4 $\frac{1}{4}$ s, 1938 | 3,079 69 |
| 2,000 | U S Treasury, 4s, 1944-1954 | 1,998 13 |
| 20,000 | U S Treasury, 4 $\frac{1}{4}$ -3 $\frac{1}{4}$ s, 1945 | 19,887 50 |
| <u>\$65,000</u> | | <u>\$64,986 06</u> |

CIRCULATION OF ANNALS OF INTERNAL MEDICINE

In compliance with the regulations of the Code Authority for the Periodical Publishing and Printing Industry (A-3), the American College of Physicians, publishers of the ANNALS OF INTERNAL MEDICINE, presents the following statement concerning the circulation of said journal for the period beginning July 1934, and ending December 1934

| | |
|------------------------------|-------|
| Average gross circulation | 3,229 |
| Average net paid circulation | 3,101 |

Subscribed and sworn to by E R LOVELAND, Executive Secretary of the American College of Physicians, this fifteenth day of March, 1935

My commission expires January 24, 1937

(SEAL)

GEORGE E NITZSCH, *Notary Public*

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MARROW INSUFFICIENCY ¹

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By reason of its wide dispersion through the body the bone marrow is not ordinarily viewed as an integral organ, yet such it is, and an extremely interesting and important one in the light of its manifold functions. Its hematopoietic activity in the formation of erythrocytes, leukocytes and thrombocytes is generally appreciated, but its wealth of reticulo-endothelium determines certain further functions that are less widely understood. Bile pigment is formed in great amounts in the marrow. Antibodies are likewise developed through reticulo-endothelial activity. However, particular attention in the present relation is directed toward the commoner cellular elements of the circulating blood which have their origin in the bone marrow ¹.

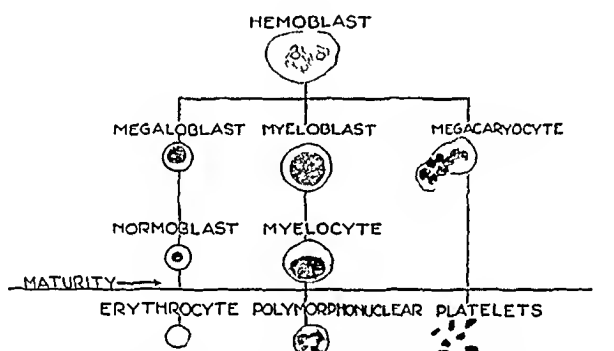
Under normal conditions the bone marrow is the sole source of the erythrocytes, polymorphonuclear leukocytes and thrombocytes in adult life. During fetal existence the liver, spleen, and lymph nodes participate in this function. Reversion to complete hematopoiesis on the part of the liver and spleen occurs only under unusual circumstances in extrauterine life. At birth, the functioning red marrow occupies the entire shafts of the long bones. By the sixteenth year, active marrow is found in the ends of the long bones, in flat bones, and in small, spongy bones. Attention on the part of students of blood dyscrasias to this normal recession of myeloid activity would eliminate much misleading detail from the literature. In general, biopsy and necropsy studies of sternal and rib marrow will afford much more accurate information of the essential disease process and myeloid state in the adult than will the marrow from the shafts of long bones.

There is no complete agreement as to the histogenesis of the mature blood cells arising in the bone marrow. The generally accepted course is represented in figure 1. The root cell, or hemoblast, is held responsible for the development of the polymorphonuclear leukocytes, erythrocytes, and platelets. Consensus of hematologists holds to the existence of special precursors in the myelocytic series for each of the granular forms of polymorphonuclear leukocytes, neutrophilic, eosinophilic and basophilic. The

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megakaryocyte of the marrow is believed to be the sole source of the thrombocyte, but under disease conditions these large cells may appear in other than myeloid tissue² Authorities differ widely in their opinions as to the development of the red blood cell series Many claim that there is no relationship between the megaloblast and the normocyte or erythrocyte This group maintains that there exists a precursor of relatively proportional size for each mature red blood cell, macrocyte, normocyte, and microcyte For the present purpose, at least, the question would appear highly academic

Two mechanisms of delivery of the cellular products of marrow activity into the circulatory blood stream have been invoked, namely, ameboid movement of the involved cells and extrusion by growth pressure Certain histologic and anatomic features of the bone marrow indicate a close relationship between structure and function There is no true capillary network



SCHEMATIC REPRESENTATION OF DERIVATION OF COMMON BLOOD CELLS FROM THE PRIMITIVE BONE MARROW CELL

FIG 1

The arterial capillaries of the marrow are relatively long and, without side branches or anastomoses, open directly into venous sinusoids or sinuses The lining endothelium of the latter is very tenuous From these conditions the resultant sluggish blood flow and the thin endothelial barrier favor the ready delivery of blood cells from the marrow to the circulation Then, too, the more or less actively proliferating marrow is encased in the inelastic bone This inelasticity is further enhanced by the semifluid yellow marrow which fills the major portion of the long bones This circumstance, while encouraging ameboid movement toward the venous sinuses, is especially important in giving direction to growth pressure

The ameboid activity of the polymorphonuclear elements becomes increasingly more marked with maturity, and this mode of migration is generally accepted as operative in the delivery of this group of white blood cells from the bone marrow to the blood The blood platelets are also known to possess ameboid movements, but apparently the factor of growth pressure is the potent one in the delivery of the erythrocytes "The vis a tergo which

pushes the cells into the blood stream is the increased extravascular pressure caused by division of the mother cells of this group" ¹⁰

The energizing force to hematopoiesis may be a common one for all types of marrow-derived blood cells, or there may exist separate stimuli for the several blood elements. Chemotaxis is believed to play an important rôle in leukogenesis. Most of the infectious processes, particularly those of coccal origin, are attended by a leukocytosis of the neutrophilic order. Hemorrhage stimulates the production of blood platelets. The work of Minot and Murphy,³ Peabody,⁴ Castle,⁵ and others has greatly advanced the knowledge of erythropoiesis by establishing the relationship of gastric physiology and certain dietary elements derived from proteins to the normal maturation of the megaloblasts of the bone marrow. This concept has been carried a theoretic step further by Witts⁶ who maintains that vitamin C, thyroxin, iron, and traces of other metals are required to change the normoblast to the mature erythrocyte. Especial interest in the present connection relates to the normal stimulus to erythropoiesis. Granting the validity of the revolutionary observations above related, Bunting's contention of a constant tempo of red blood cell production ¹⁰ still appears sound. He holds that a given quantum of bone marrow can only produce erythrocytes at a given rate. For an increased production there must occur an extension of the erythrogenetic centers. So far as is known, lowered oxygen tension constitutes the only normal stimulus to the extension of the bone marrow.⁷

Depression of hematopoiesis has long been recognized in diseases intrinsic and extrinsic to the bone marrow. This circumstance may arise from a primary disease of the myeloid system, or this important structure may be secondarily involved. The earliest available reference to the term, marrow insufficiency, by Vaquez and Aubertin,⁸ follows "*Étant donnée cette absence complète de réaction myéloïde, nous fûmes amenés à penser que les organes hématopoïétiques étaient incapables de former des globules rouges nouveaux, et nous portâmes—avec quelques réserves cependant—le diagnostic d'anémie pernicieuse avec moelle jaune, c'est à dire avec insuffisance médullaire*"*. Obviously, from the clinical course and the pathologic findings, these observers were dealing with a case of aplastic anemia in an adolescent offspring of a syphilitic and alcoholic parent. Their further analysis of the anemias by the bone marrow responses is illuminating. "Orthoplastic" anemia succeeds hemorrhage, and the marrow shows a normal response with some changes in the form and staining reaction of the erythrocytes, and a few nucleated forms appear in the peripheral blood. "Metaplastic" anemia is best exemplified in pernicious anemia where many nucleated red blood cells are seen, and megaloblasts and other signs of immaturity are not uncommon. Finally, the "aplastic" type is described as

* Because of this complete absence of myeloid reaction we were led to infer that the hematopoietic organs were incapable of forming new red blood cells, and we made the diagnosis—with some reservations—of pernicious anemia with yellow bone marrow, that is, with marrow insufficiency.

*"un état fonctionnel insuffisant héréditaire ou acquis des organes hématopoïétiques" **

Aplastic anemia was first recognized as a clinical entity by Ehrlich⁹ in 1888. Most of the reported cases have resulted from exposure to the toxic action of radium, roentgen-ray, benzol, or arsphenamine. Occasionally an infectious process may lead to total paralysis or insufficiency of the bone marrow. In rare instances aplasia may appear in the course of an Addisonian anemia. Finally there remains an idiopathic type in which no etiologic background can be ascribed. The clinical course of the so-called idiopathic aplastic anemia is usually terminated by death within three months from the outset regardless of therapy. It occurs most frequently between the ages of 15 and 30 and more commonly in the female sex. A waxen pallor supervenes. Of particular differential value are the blood studies. The characteristic absence or extreme paucity of evidences of regeneration is the most important single detail. There may be little change in the individual erythrocytes. As contrasted with pernicious anemia, no signs of hemolysis are detectable. Leukopenia is the rule. The neutrophils are especially decreased and a relative lymphocytosis results. The platelets are reduced. By reason of the thrombocytopenia, purpuric manifestations sooner or later complicate the anemic picture. Accordingly, in order, all of the marrow-derived blood cells are depleted in the peripheral circulation. As might be anticipated, a strikingly acellular yellow marrow is found at necropsy in all but a few exceptions.¹⁰

CASE I

F W, a white German-born woman of 38, entered the hospital with a chief complaint of progressive weakness of six weeks' duration. Questioning elicited the further complaints of increasing pallor, headaches frequently during the two months before admission, occasional tinnitus and vertigo, rather easy bruising but no spontaneous subcutaneous hemorrhages, one recent nose-bleed and occasional slight streaking of the sputum with blood. The patient worked as an ironer in a laundry. In an adjoining room carbon tetrachloride was used for cleaning. There were some fumes of carbon tetrachloride permeating her work-room, but she had no direct contact with any chemical. No fellow-employees experienced similar complaints and the family history was negative in this direction. The social and past histories were otherwise irrelevant.

The pertinent physical findings were moderate obesity, pallor of the skin and mucous membranes, three small petechial hemorrhages in the mucous membrane of the mouth, soft systolic murmur at the cardiac apex, slight edema of the lower extremities, small ecchymotic areas on the right arm and thigh and a few hemorrhages in the optic fundi.

The laboratory examinations included an urinalysis showing a slight trace of albumin and an occasional white blood cell. The blood chemical tests were normal, and the blood Wassermann test negative. The blood count showed a hemoglobin of 20 per cent, erythrocytes 1,570,000, leukocytes 3,600, neutrophils 38 per cent, eosinophils 4 per cent, and lymphocytes 58 per cent. Platelets were moderately decreased.

* A state of functional insufficiency of the hematopoietic organs, of either hereditary or acquired nature.

Bleeding time was 12 minutes, clotting time, 2 minutes. The fragility of the red blood cells was normal. Gastric analysis after histamine showed an absence of free acid. Stool examinations were negative.

During residence in the hospital, for 88 days, the patient had several small nose-bleeds. Moderate fever existed irregularly. The patient was given liver extract 343 (Eli Lilly) for two weeks without improvement. Likewise, the daily administration of 90 grains of ferrous carbonate for over a month was without demonstrable effect. After repeated transfusions, the hemoglobin on the seventy-third hospital day was 51 per cent with 2,750,000 erythrocytes. Thereafter there was progressive decline in the red count and hemoglobin, and she was not capable of maintaining a level despite repeated transfusions of 500 c.c. of blood. During her residence in the hospital the patient had a total of 18 blood transfusions, each 500 to 600 c.c. in volume. Toward the end of her course, after four transfusions on four consecutive days, the hemoglobin was 31 per cent and the red blood cells numbered 1,700,000.

On the eighty-eighth day the patient's condition suddenly became alarming, there were hemorrhages from the gums, pulmonary edema supervened, subcutaneous edema rapidly became generalized, and the patient expired.

The postmortem examination showed hemorrhages into the gums, myocardium, ovary, and mucosa of the stomach, intestine and bladder, enlargement of bronchial lymph nodes, terminal bronchopneumonia, cardiac hypertrophy and dilatation, and an aplastic bone marrow. Microscopic examination showed hemorrhage in the lungs and in the bronchial lymph nodes in addition to the above mentioned sites. Microscopic examination of the bone marrow confirmed the gross evidences of aplasia.

The primary diagnosis was aplastic anemia of undetermined origin. The inconsiderable exposure to carbon tetrachloride probably played no part in the picture. The early hemorrhagic tendency bespoke a failure in the platelet formation as well as in erythropoiesis. The clinical course, laboratory, and necropsy findings sustained the primary diagnosis of an idiopathic aplastic anemia.

In a number of cases of aplastic anemia the impression of a congenital deficiency is gathered. Predtechensky¹¹ holds that congenital hypoplasia of the bone marrow is the precursor of primary aplastic anemia in event of an unusual demand for myeloid activity. Minot¹² entertains the same thesis in explanation for certain borderline cases between aplastic anemia and purpura hemorrhagica but prefers the designation, insufficiency of the marrow, with a qualifying phrase as to the particularly deficient element or elements. Rennie¹³ suggests "that aplastic anemia in young persons is the result of the exhaustion of function of a bone marrow congenitally defective in power of endurance." In a different relation Miloslavich and Murphy¹⁴ refer to the "constitutional (functional) inferiority of the bone marrow" that becomes completely exhausted under demand. Case 2 presents such a problem in pathogenesis.

CASE II

E. G., a 63-year-old woman, herein considered through the courtesy of Dr. Frank L. Weston, gave the following story. All of her life she had had ecchymotic areas in the subcutaneous tissues after slight injuries. At times, even wiping the hands with a towel would produce hemorrhagic areas in the skin. Bleeding from the gums usually attended brushing of the teeth. Interestingly and pertinently, her

mother and sister were similarly affected. The patient had experienced colds and tonsillitis many times. Ten years before admission she had a rather profuse hemorrhage for three or four hours following dental extraction. Two weeks before admission the patient noted numerous purpuric areas over the legs, arms, and shoulders. At the same time there was spontaneous bleeding from the nose and gums. There had been no fever, pain or soreness, and there was no known bleeding from any of the viscera.

The past medical history brought out nothing of importance. The menopause had occurred 13 years before.

The physical examination showed a fairly well developed and nourished female in apparent distress. Pallor was marked and over the limbs there were hundreds of subcutaneous hemorrhagic areas ranging from pinpoint to hand size. There were also some hemorrhagic areas on the face and trunk, one petechia in the conjunctiva and some in the oral mucous membranes. There was intranasal crusting due to dried blood. Of the two hemorrhagic areas on the tongue, the larger was 1 by 3 cm in size. The lungs were clear, there was a systolic murmur localized to the cardiac apex, the blood pressure was 180 systolic, 102 diastolic. There was no adenopathy, and the spleen was not enlarged. On admission, the temperature was 100, pulse rate 120, respirations 22.

The laboratory examinations on admission showed a normal urinalysis, the non-protein nitrogen and blood sugar within normal limits, blood Wassermann negative, stool examination positive for blood. The blood showed a hemoglobin of 55 per cent, erythrocytes 3,190,000, leukocytes 3,300 with 31 per cent neutrophils, 3 per cent eosinophils, 62 per cent small lymphocytes and 2 per cent large mononuclears. Blood platelets numbered 40,000. The coagulation time was $3\frac{1}{2}$ minutes, bleeding time 40 minutes.

During residence in the hospital, the patient's course was that of progressive decline. A fever, reaching a daily peak of from 100 to 101° F, was the rule, and on the last two days before death the temperature rose to 105.2° each evening. Blood appeared in the urine on the third day after admission. After four transfusions of cross-matched, group IV (Moss) blood, the hemoglobin rose to 70 per cent, erythrocytes 4,280,000. The leukocytes ranged between 1000 and 2000 for the week before death, and there was always a relative lymphocytosis. The leukopenia had become more marked as the disease progressed, and reached a low level of 750 with 100 per cent lymphocytes on the day of death. The day after the second transfusion, the platelet count was 240,000, but save for one other day, again after a transfusion, the platelet count was invariably below 100,000 and most of the 16 days in residence the platelet count was between 20 and 40,000.

The postmortem examination showed in addition to multiple hemorrhages in the skin, lungs, pleurae, pericardium, stomach, kidneys, and bladder, a chronic gastritis and colitis, acute ulcers of the ileum and colon, pulmonary infarcts and in the main, an aplastic bone marrow. The rib marrow showed death of the leukogenetic centers, the erythrogenetic centers showed some nucleated red cells and intermediate types. The marrow was fatty, there was congestion and hemorrhage and an absence of megakaryocytes.

The final primary diagnosis was aplastic anemia. The etiology was undetermined. Dr C H Bunting, who examined the microscopic sections, emphasized the existence of the gastritis and colitis and considered these abnormalities as possible etiological factors. Gastric analysis had not been made because of the patient's serious condition.

The hemorrhagic tendency in other members of the family raises the question of a congenitally defective bone marrow in this patient. Having

experienced a purpuric tendency from early life, the terminal course of her blood picture would suggest a progressive failure of the bone marrow to produce all of the common myeloid elements. After the sharp exacerbation of the chronic platelet deficiency, as manifest by the unusual bleeding, the marked anemia indicated an inhibition of the erythrogenetic function of the marrow, and finally the absolute neutropenia rendered the picture of marrow insufficiency complete in the failure of the leukogenetic centers.

In the so-called idiopathic aplastic anemia the prognosis is universally grave. A few subjects have experienced short remissions and then relapsed to a fatal termination as in the case reported by Lariabee.¹⁴ Lescher and Hubble¹⁵ collected five instances from the literature in which remissions had occurred in the course of aplastic anemia. Two of this series relapsed to death. No form of treatment avails. Gottlieb¹⁷ performed a splenectomy upon a single patient with aplastic anemia or "complete myeloid insufficiency." An incomplete remission ensued and in spite of the fatal outcome, certain hematopoietic returns in his opinion justify a further consideration of the principle involved. Rendu and Widal¹⁸ maintain that overactivity of the splenic function depresses the bone marrow. Their hypothesis is built upon a single case in which polycythemia attended tuberculous splenomegaly, and they admit the experimental and clinical evidence to the contrary in the absence of a polycythemia after splenectomy. Gottlieb¹⁷ cites more substantial evidence of the inhibitory effect of the reticulo-endothelial system upon the marrow, as, for example, the leukopenia, anemia, and purpura that attend typhoid fever, influenza, and other infections with reticulo-endothelial hyperplasia.

The appreciation of general marrow insufficiency leads naturally to a consideration of the possible independent or selective involvement of one or the other of its component elements. Minot,¹² Rosenthal,¹⁹ Lescher and Hubble,¹⁵ Aubertin²⁰ and Gil²¹ among others have indicated the liability of the several circulating blood cells to suffer independent depletion as a result of selective depression of their centers in the bone marrow. The growth of this viewpoint may be traced in a chronologic investigation of the literature. As a direct outgrowth of this movement, certain clinical entities have been evolved, but there remain many borderline cases that demand attention. Clearly, in the light of the histogenesis of the several blood cells an overlapping of the resultant hematologic pictures may be anticipated. Many terms have arisen to express such combinations. The *aleukia hemorrhagica* of Frank²² is such an example. As the author explains, there is primarily a "myelotoxikose" with a secondary anemia, partially posthemorrhagic and partially myelophthisic. On careful analysis it would not appear a justifiable deviation from the generic term, aplastic anemia. The marrow biopsies of Falconer and Morris²³ indicate that invaluable though such studies may be, they are not infallible in the differentiation and definition of the basic fault. They plead for a more flexible nomenclature in contrast to Witts¹⁰ who deems it "best to group all these cases under the broad heading

of aplastic anemia, as the leading feature in all is absence of regeneration on the part of the bone marrow "

The consideration of the clinical syndromes dependent upon failure of hematopoiesis in a single element of the marrow opens a number of interesting questions. The entire subject has been comprehensively treated by Lescher and Hubble,¹⁶ who point out the striking infrequency of pure red cell anemia. They found only three cases in the literature. From a theoretic as well as a working viewpoint, the term, anerythropoietic is here-with suggested, for this limited group in which only the erythrocytic centers suffer. Such a designation is an obvious adaptation of Hayem's *anémie par anhématopoïèse* which Aubertin²¹ thus described "*C'est pour quoi, quand on parle aujour d'hui d'anémie par anhématopoïèse, il s'agit d'anémie par insuffisance de la moelle osseuse ou plus exactement du tissu myéloïde, insuffisance totale ou partielle, ou même simple déviation fonctionnelle de ce tissu*" *. Unquestionably a majority of such patients pass into a more or less complete marrow failure with a resultant picture of idiopathic aplastic anemia as Aubertin²⁴ suggests.

Greater opportunity to study the results of the depression of thrombocytopoiesis and of leukopoiesis has been afforded by the more abundant clinical materials. The reduction of the blood platelets may occur from many causes. In the present relation only essential thrombocytopenia is considered. The most conspicuous detail in its clinical picture is the hemorrhagic tendency. Minot¹² sets 60,000 per cubic millimeter as the critical level below which reduction of the platelets is attended by bleeding. In the purpura hemorrhagica that attends this condition, bleeding occurs into the skin and mucous membranes with frank epistaxis, hemoptysis, hematemesis, melena, hematuria at times. Menorrhagia and metrorrhagia present serious problems in blood loss in females with this condition. Cerebral hemorrhage is not common. From the laboratory viewpoints in addition to the more or less marked reduction of the platelets, a hypochromic anemia is the rule. The bleeding time is almost invariably prolonged. The clotting time is approximately normal. The resultant coagulum is poor in texture and retracts very inadequately. The tourniquet test, although commonly positive, offers little aid in diagnosis because of its presence so widely in hemorrhagic affections. Falconer and Morris²³ question the wisdom of marrow biopsies in purpura hemorrhagica.

The following case is a classical instance of thrombocytopenia in all essential details.

CASE III

E. T., a white female aged 27 years, was first seen in consultation with the late Dr. Louis R. Head in January 1929. Throughout her life she had remarked easy bruising upon slight trauma. Two paternal cousins had a similar tendency, and one

* Therefore when we speak now of anemia due to an hematopoiesis we mean anemia due to insufficiency of the bone marrow or more exactly of the marrow tissue, and this insufficiency may be total or partial, or even be only a functional deviation of this tissue.

had had a splenectomy to remedy this condition. The patient's present complaint was dated to June 1927, when she had first observed profuse menstrual bleeding. Ten to twelve pads had been used daily through each menstrual cycle since that time. In December 1928, the patient had suffered an attack of influenza, and after about a month (or upon the initiation of the next menstrual cycle) there was profound menorrhagia succeeded by severe and recurrent epistaxis. Shortly thereafter appeared large purpuric areas over both legs and smaller ones on the arms. The mucous membrane of the mouth was studded with similar lesions.

The failure of minor measures to control the situation and the development of a profound anemia led to her admission to the Madison General Hospital on January 29, 1929.* The blood count on January 28, 1929, immediately before entrance, was as follows: Hemoglobin 45 per cent, erythrocytes 1,750,000, leukocytes 9,000, differential count, neutrophils 81 per cent, eosinophils 1 per cent, lymphocytes 15 per cent, mononuclears 3 per cent. The platelets were observed to be very markedly reduced in this study and the first numerical count was recorded three days later as 40,000 per cubic millimeter. The trend of these elements through the two periods of hospitalization is plotted in figure 2.



FIG 2 The curve of the blood platelets in Case 3

Particular attention is directed to the very transient advantage of the repeated (5) transfusions during the first period of hospitalization. Although bleeding was controlled at this time, with the next menstrual cycle all of the purpuric manifestations recurred in an aggravated form. Whereupon no material benefit in the bleeding tendency resulted from the multiple (8) transfusions which merely served the purpose of modifying the severity of the anemia through replacement. Subsequent to the

* We are indebted to Dr. Lester McGary for the laboratory studies during the patient's stay in this institution.

splenectomy performed by Dr N M Percy of Chicago, the platelets rose from 10,000 to 118,000 on the first day, and to 299,000 on the second day postoperatively. This level was not maintained, for a week after the operation the platelets numbered 55,000 and 10 days later (17 days postoperatively) 24,400. Nevertheless, the control of bleeding was spectacular. For the first three days after the operation there was a small amount of vaginal bleeding. Thereafter, none appeared. On the ninth day postoperatively there was a slight epistaxis which was easily controlled.

Dr Lester McGary gave the following description of the spleen. The organ measured 13.5 by 6.5 by 4.5 cm and weighed 195 gm. The capsule was smooth and moist and of normal thickness. Two small infarcts, size of ten-penny nail, were seen on the anterior inferior surface. The cut surface was smooth and reddish brown in color. The Malpighian corpuscles and trabeculae were distinct. Sections showed an increase in endothelial cells and eosinophiles.

A year of freedom from any purpuric manifestations followed the splenectomy. Then in March 1930, menorrhagia recurred and purpuric spots appeared on the arms, hands, forehead, and neck. Interestingly this episode succeeded a period of intensive whole liver therapy. On April 1, 1930 she was admitted to the Wisconsin General Hospital where the platelets were found to number 30,000 per cubic millimeter. A transfusion of 500 cc of whole blood caused a sharp reaction with the temperature rising to 104° F. Thereafter the platelets ranged from 60,000 to 150,000, and the patient was discharged on April 16 with the hemorrhagic tendency under control.

During the ensuing two years she was under constant observation, and at no time was there a relapse in the blood picture or evidence of unusual bleeding. The platelets mounted as high as 310,000 on July 6, 1931, and at no time fell to critical levels. The menstrual flow remained rather scanty. Her activities were gradually extended, and after consultation and complete discussion as to the hazards, pregnancy was sanctioned early in 1932. The platelets were followed closely through gestation and ranged from 110,000 to 140,000 until the day before delivery when they fell to 50,000. Apparently coincident with this decline in the platelets, there appeared many purpuric spots over the face and body. Ten days after delivery, the mother's platelets had mounted to 140,000, and five weeks later to 220,000. Subsequent to this time there has been no recrudescence in the purpura. The baby was normal in all details.

This patient represents a clear-cut example of thrombocytopenic purpura of the idiopathic variety since no cause could be determined. The response to splenectomy was truly dramatic, and, as pointed out by many observers, the resultant advantage was maintained even though the platelets fell to precarious levels shortly after the operation. The relapses, a year postoperatively and immediately before parturition, were quite transient. The first episode apparently responded to the severe transfusion reaction. In any event this circumstance initiated the improvement which held the hemorrhagic tendency in check until just before delivery. Whatever may have been the factors determining the very transitory purpuric manifestations on the latter occasion, there was no unusual bleeding at parturition and no occurrence of the purpura thereafter. To the present time there has been no further recurrence of the bleeding.

The prognosis of essential thrombocytopenia varies widely. At times simple measures in hemostasis will tide over relatively slight episodes of bleeding. Again transfusions will meet the exigencies of the given case. It is well to remember that the life of the platelet is three to five days¹². Hence, an advantage prolonged for an interval exceeding this short period

after transfusion must be attributable to the patient's own recuperative powers. Minot¹² points out that, as a rule, if the marrow fails completely, the platelets will be the first element to disappear from the circulating blood.

The treatment of thrombocytopenia is by no means standardized. Dietary measures, liver, vitamins, especially A, B, and C, vitaminol, minerals, including iron and calcium, and ultra-violet light therapy have been recommended. A rational regimen of living and eating seems reasonable, but no specific virtue has been found in any single therapeutic agent. Splenectomy is indicated upon the failure of simpler means to control the fundamental fault. It should not be withheld until the hazard of the operation is overwhelmingly increased by the gravity of the bleeding or the anemia. Leukopenia and the absence of active hematopoiesis are relative contraindications to splenectomy in this condition.¹⁶ Ligation of the splenic artery has not been universally successful as a substitute for removal of the spleen.²⁵ Roentgen-ray therapy over the splenic areas has not satisfactorily supplanted splenectomy in the experience of most clinicians. The favorable responses to splenectomy are not uniform. Christian²⁶ believes it impossible to predict the outcome of the operation. It should, nevertheless, be given full consideration with the reservations as stated.

Failure of leukopoiesis was first reported as a clinical complication of severe sepsis by Turk²⁷ in 1907. It has been recognized as a portent of serious marrow insufficiency in overwhelming infections since that time. The clinical syndrome of agranulocytosis or agranulocytic angina was described and named by Schultz²⁸ in 1922. For a time a controversy waged as to the sequence of events. At present, it is generally accepted that necrosis occurs subsequent to the depletion of the circulating neutrophils. In a number of reported instances a neutropenia has developed some days antecedent to the appearance of the anginal symptoms. In the typical case there appears a period of malaise and physical depression before the frank febrile bout. Then the patient becomes markedly prostrated, the temperature rises to 101 to 105° F, and areas of necrosis appear in the mouth, rectum, or vagina. The draining regional lymph nodes may become enlarged, but general lymphadenopathy and splenomegaly are not the rule. The blood picture is extremely interesting. In a majority of cases the leukocyte picture alone is affected. Philipschenko²⁹ proposes three groups of cases with failure of leukopoiesis, but his inclusion of patients with anemia and with anemia plus hemorrhage involves the consideration of the complicated pictures, previously discussed. Weber³⁰ also maintains that there is no definite boundary between agranulocytosis and aplastic anemia, but as a matter of fact, the usual neutropenia shows neither anemia nor hemorrhagic tendency. At times an advanced or terminal case may evidence extension of the marrow insufficiency by these manifestations. The usual patient with neutropenia shows a gross decrease to total absence of these marrow-derived granular elements. The course of the basic condition may be traced by the percentage and numerical figures for the neutrophilic

polymorphonuclear leukocytes With their continued depletion there is serious danger of complicating pyogenic processes in the lungs and urinary tract as well as the above mentioned necrosis in passages directly connected with the exterior The dependence of the mucous membranes of the mouth, rectum, and vagina upon the mobile protection of the neutrophiles is in no manner better attested than in the rapid healing of necrotic areas in these locations upon the reappearance of the missing or deficient white blood cells As a rule the bone marrow shows little or no leukogenetic activity at the height of the neutropenia, but Fitz-Hugh and Krumbhaar³¹ have established cases of neutropenia with definite leukopoiesis in the marrow They postulate the probable occurrence of a failure of maturation and delivery of the neutrophiles from such centers

Especial interest in the neutropenias centers about the surpassing contribution of Madison and Squier³² to its pathogenesis In a well-controlled series of cases these clinicians establish the unquestionable responsibility of amidopyrine for a certain number of the neutropenic reactions They feel that the neutropenia is a sensitization to the drug and that there are, of course, other and varied causes for the same failure in leukopoiesis by the bone marrow

The following case quite vividly illustrates their position relative to amidopyrine's responsibility

CASE IV

R R, a white school-boy, 13 years of age, apparently slowly convalescing from rheumatic fever, was admitted to the Wisconsin General Hospital The history was important only in the detail of the polycyclic order of the arthritic manifestations The physical examination disclosed cryptic diseased tonsils, carious teeth, an apical systolic thrill and murmur, swelling, heat and redness of both knees Studies of the blood revealed a minor degree of secondary anemia (erythrocytes 4,500,000, hemoglobin 70 per cent) and a slightly elevated white cell count (9,880 with 63 per cent neutrophiles) The early stay in the hospital was marked by satisfactory progress in the arthritic involvement, occasional slight elevations of temperature not exceeding a degree and improvement in the general condition for 28 days

On the twenty-ninth day the patient experienced listlessness general malaise, fever, and chills There appeared an irregular, inconstant blotching of the skin, puffiness of the eye-lids and redness of the oro-pharynx The temperature rose to 102° F The leukocyte count, on the thirty-second day, was 10,300 with 51 per cent neutrophiles, 43 per cent small lymphocytes, 1 per cent large lymphocytes and 5 per cent large mononuclears

In the belief that these manifestations represented a rheumatic recrudescence, amidopyrine was administered in doses of 5 grains four times a day On the fourth day of this therapy and after a total of 45 grams, the patient complained of severe epigastric pain, and the temperature rose to 105.4° F A number of petechiae appeared in the soft palate, the abdomen was tender and resistant, especially high in the epigastrium, the liver was palpable 4 cm below the costal margin, the skin showed a blotchy macular eruption The leukocytes numbered 3800 with 40 per cent neutrophiles, 52 per cent small lymphocytes, 5 per cent large mononuclears, and 3 per cent metamyelocytes Thereafter, leukocyte and differential counts were made twice a day The curve is plotted below (Figure 3)

It will be observed that the marrow-derived white cells reached their lowest level on the day after the discontinuance of amidopyrine with 1 per cent neutrophils and 6 per cent metamyelocytes, or 322 marrow-derived white cells in a total white cell count of 4600. The complete disappearance of neutrophils two days later, when the total leukocytes numbered 3,350, was attended by the sharp accession in metamyelocytes, 23 per cent, or a total of 770 cells of marrow origin. In evaluating the influence of pentnucleotide in the result graphed above, the initiation of the myeloid reaction within 48 hours after the institution of this therapy anticipated the usual response which is not expected for 96 hours. This advantage was maintained, and

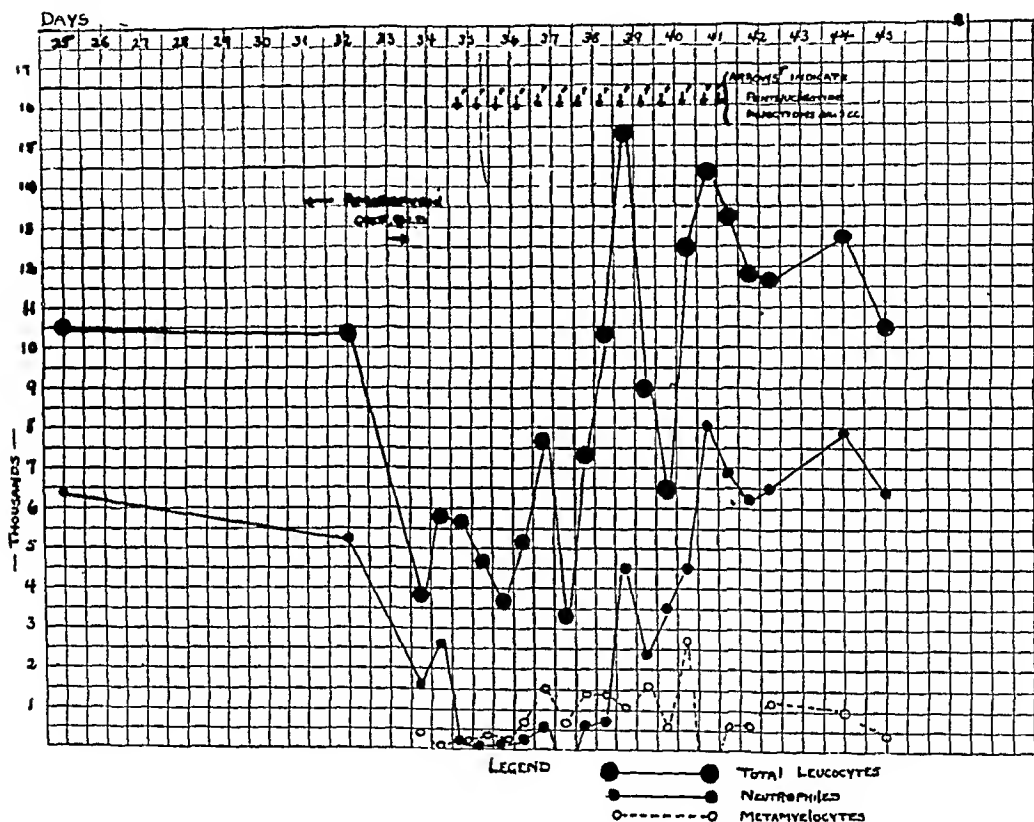


FIG 3 The leukocyte curves in Case 4

the temperature subsided to normal on the fourteenth day after the beginning of the neutropenic reaction. It is important to note that subsequent to a tonsillectomy on the ninety-second day of hospitalization, there was a reactive leukocytosis of 22,000, with 70 per cent neutrophils.

This patient falls into the increasing group of neutropenias dependent upon a sensitivity to amidopyrine. The efficacy of pentnucleotide in this particular instance may be seriously questioned. In the first place, many reported cases of neutropenia of this order have recovered spontaneously and rapidly upon the withdrawal of amidopyrine. Furthermore, the initial evidence of leukogenetic response was remarkably prompt for a pentnucleotide effect. The apparently complete recovery of the leukogenetic centers

in the bone marrow is at least suggested by their later adequate response on the occasion of the tonsillectomy

The prognosis in neutropenia depends in a considerable measure upon the existence of a recognizable and recognized cause. As remarked before, in subjects sensitive to amidopyrine, its removal is attended by prompt and maintained recovery. Idiopathic or essential neutropenia may undergo spontaneous or induced remissions. There is no regularity in the occurrence or duration of such remissions. Pentnucleotide in intramuscular doses of 10 cc twice daily is recommended³³. Its administration must not be too early interrupted, since serious relapses may occur under these circumstances. The results in relapsing cases are frequently discouraging. Every precaution should therefore be taken to forestall serious declines in the circulating neutrophils by appropriate doses of pentnucleotide. Adenine sulphate has given results similar to those attributed to pentnucleotide³⁴. In the opinion of most students of the subject, small transfusions are of no specific value in neutropenia and large transfusions are contraindicated. Roentgen-ray in small doses has been advised by certain observers but others seriously question its efficacy.

In conclusion, the clinical expressions of marrow insufficiency should always be borne in mind in the analysis of the blood dyscrasias. This important organ may fail as a unit, in which event the picture of aplastic anemia supervenes. Or any of its functional and histologic components may fail separately. Anergic,thropoietic (red blood cell) anemia is the rare condition, in which only the erythrocytic function of the marrow is depressed. Thrombocytopenia results from the failure of the formation of blood platelets. Neutropenia may reflect a leukogenetic failure of the marrow. Lescher and Hubble¹⁶ suggest the terms, myelophthisis, thrombophthisis, and granulophthisis, for aplastic anemia, thrombocytopenia, and neutropenia, respectively. These several clinical entities are interrelated, and their pictures may blend, but in the interest of clarity, they should be considered separately. Their pathogenesis and treatment take on peculiar significance from such an approach, and the solution of certain difficult problems in clinical hematology is promised thereby.

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III THE METABOLIC ASPECT OF ASSOCIATED DIABETES MELLITUS AND PULMONARY TUBERCULOSIS¹

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THE association of tuberculosis and diabetes has attracted the attention of many authors and has been the subject of numerous case reports[†]. During the past five years, 80 patients presenting this combination of diseases have been under observation in Herman Kiefer Hospital, Detroit. A statistical analysis of the clinical features, prognosis and treatment of the tuberculosis as well as detailed reports of several cases have been published recently^{4,5}. Since there is no general agreement regarding the management of the diabetes complicated by tuberculosis and the effect of the pulmonary process upon the carbohydrate metabolism, we have felt that our experiences warrant discussion.

Selection of Cases Thirty-two of the 80 cases were selected for nutritional study. Each of this group was under observation in the hospital for six or more consecutive months, the average length of stay being 555 days. All seldom or never refused any portion of the meals served to them and none, we believe, obtained additional food elsewhere. Limitation of the group selected for nutritional studies in this manner was considered necessary to minimize the many sources of error inherent in clinical work of this type.

The group included five in the third decade of life, six in the fourth, ten in the fifth, eight in the sixth, and three in the seventh. The sex distribution was about equal, there being 15 males, and 17 females. Twenty-six were white and six were colored.

CLINICAL FINDINGS

Symptoms of Diabetes The most frequent complaints were weakness and loss of weight, presumably because they are symptoms common to both diseases. Twenty-nine patients complained of weakness, 25 had lost more than 5 kg (11 lbs) in weight, the appetite, however, was preserved or increased in 24. Eighteen patients had had polydipsia and polyuria prior to entry, suggesting that the diabetes was grossly out of control.

Symptoms and Signs of Tuberculosis The incidence of fever, night sweats, pleurisy, cough, sputum and hemoptysis in the entire group of 80 cases was given in a previous publication⁴. It was found that these symp-

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[†] Those in search of a review of the literature are referred to the articles of Root,¹ Banyai² and Scholz.³

toms occurred about as frequently in this series as in nondiabetic tuberculosis. Likewise the physical signs were in accord with the roentgen-ray findings in the majority of cases. The high incidence of symptoms and pathognomonic signs is contrary to the experience of Joslin⁶ who stated that tuberculosis comes on more insidiously in the diabetic than in the general population. These differences in opinion may be due to differences in the type and extent of the tuberculosis. The pulmonary process in 27 of our cases was classified by the admission roentgen-ray as far advanced and in five as moderately advanced. The lesion was predominantly exudative in six, productive in 11, and mixed in 15. Cavitation was demonstrable in 29 of the 32 cases. Tubercle bacilli were found in the sputa of all but two patients, both of whom had had positive sputa previously at another hospital.

Laboratory Urine examinations were made daily. In all of those consistently sugar free, 24 hour specimens were obtained. When there was a persistent or intermittent glycosuria, quantitative analysis was made on four fractional specimens, collected as follows: (1) from breakfast to dinner, (2) from dinner to supper, (3) from supper to bedtime, (4) from bedtime to breakfast. Blood sugars were taken at least once weekly in the following rotation: first week, before breakfast, second week, 2½ hours after breakfast, third week, 2½ hours after dinner, fourth week, before breakfast, etc. The Folin-Wu method of analysis was used. The diabetes was considered under control when the urine was constantly sugar free and the blood sugar was under 140 mg per cent at all of these periods. It was considered out of control when either a consistent glycosuria or hyperglycemia (above 160 mg per cent) occurred. It was regarded as under partial control when the blood sugar was between 140 and 160 mg per cent. According to these criteria, all 32 patients were out of control on admission, whereas six were partially controlled and only one was out of control at discharge. The latter, who died in the hospital, had a marked hyperglycemia and glycosuria for two weeks prior to his death. The blood CO₂ combining power, however, was 62 vol per cent on the day preceding exitus. The diabetes was controlled or partially controlled for more than three-fourths of the period of hospitalization in 11 cases, during ½ to ¾ of the period in 18 cases, during ¼ to ½ of the period in two cases and for less than ¼ of the period in one case.

TREATMENT OF DIABETES

Preparation of Diets All diabetic diets were prepared in a special kitchen under the supervision of a competent metabolic dietitian. The trays were checked by the dietitian before they were distributed to the patients and again on their return. All untouched food was weighed and replaced by something with an identical glucose equivalent. An especial effort was made to prepare palatable food and to cater to the likes and dislikes of the patients so that everything served would be eaten, leaving little temptation

to cheat. Precautions were nevertheless taken to minimize opportunities for obtaining food elsewhere. The patients were segregated from the non-diabetics in single and double rooms and were bed-fast for most of their hospital stay. Visiting hours were held four times weekly and visitors were not allowed to bring in anything edible. This latter rule was strictly enforced by the nurse escorting them to the patients' rooms.

Because of these precautions it is believed that the diets prescribed for the patients were for the most part identical with those actually consumed. The figures given for the composition of the diet represent carefully computed averages for the entire period of hospital stay.

Caloric Intake The caloric intake of each patient is indicated in table 1, the average for the entire group being 2138 calories daily, or 34 calories per kg. On the other hand, the average house diet served to the routine cases of tuberculosis contained from 2500 to 3000 calories.

TABLE I
Average Caloric Intake during Period of Hospitalization

| Total calories | 1600-1800 | 1800-2000 | 2000-2200 | 2200-2400 | 2400-2600 | 2600-2800 |
|----------------|-----------|-----------|-----------|-----------|-----------|-----------|
| No. cases | 2 | 6 | 11 | 9 | 3 | 1 |

Total Calories

| Cal. per kg | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 |
|-------------|-------|-------|-------|-------|-------|-------|
| No. cases | 0 | 5 | 14 | 9 | 4 | 0 |

Calories per Kg. Body Weight in Diet

| Cal. per kg | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 |
|-------------|-------|-------|-------|-------|-------|-------|
| No. cases | 0 | 7 | 18 | 6 | 1 | 0 |

Calories per Kg. Required to Maintain Body Weight at a Constant Level

Weight Since the caloric intake in these patients was distinctly less than is generally considered advisable in tuberculosis, the changes in body weight are presented in table 2. The patients were weighed routinely once or twice weekly under standard conditions on scales accurate to 25 kg.

As is evident in table 2, 23 were below the average weight for their height, age and sex on admission to the hospital and only four were above. A deliberate attempt was made to bring all patients to or slightly above the average. This was achieved in all but eight, six of whom are still in the hospital. The greatest weight gain during the period of hospitalization was 28.2 kg (61.5 lbs.) on a daily intake of 2290 calories. The average weight gain for the entire group was 7.4 kg (16.25 lbs.) on a diet containing 2138 calories. One patient who was considerably overweight on admission was

TABLE II
Body Weight

| | Loss | | Stationary | Gain | | | |
|----------|---------------|--------------|-------------|--------------|---------------|---------------|---------------|
| Wt in kg | -25 to -15 | -15 to -5 | -5 to +5 | +5 to +10 | +10 to +15 | +15 to +25 | +25 to +35 |
| No cases | 1 | 0 | 9 | 9 | 10 | 2 | 1 |

| Change in Weight during Period of Hospitalization | | | | | | | |
|---|----------------|----------------|---------------|--------------|----------------|----------------|----------------|
| | Below standard | | | At standard | Above standard | | |
| | -35 to -25% | -25 to -15% | -15 to -5% | -5 to +5% | +5 to +15% | +15 to +25% | +25 to +35% |
| At beginning | 4 | 8 | 11 | 5 | 3 | 0 | 1 |
| At end | 0 | 1 | 7 | 15 | 7 | 2 | 0 |

Weight in Percentage of Standard at Beginning and End of Period of Hospitalization

gradually reduced to her standard weight. This was later regretted because the tuberculosis became worse and exitus occurred.

Energy Requirements Since such comparatively low caloric diets were sufficient to permit a weight gain in most of the patients, it becomes of interest to determine the number of calories needed to maintain weight at a constant level, i.e., the energy requirement. This can be calculated roughly if we assume that all of the added weight is deposited as fat.

Such an assumption ignores the possibility that a portion of the weight increment may consist of protein tissue, water stored temporarily in the body or fecal matter retained in the colon. Since all of the patients had attained full growth and since all received comparatively low protein diets (about 1 gm per kg) we believe that the protein deposited was negligible. An average of two or three weight determinations at the beginning and end of the period was used to minimize the error introduced by fluctuations in stored water and retained feces.

For each gram of weight gained, 8.5 calories were deducted from the total amount consumed during the period of observation*. The corrected value for the total calories was then divided by the number of days in the period to obtain the daily energy requirement, which in one patient was about 1570 calories, in six ranged from 1600 to 1800 calories, in eight from 1800 to 2000, in ten from 2000 to 2200, in five from 2200 to 2400 and in two from 2400 to 2600 calories. These figures represent the basal requirement, together with increments arising from the specific dynamic action of food,

* Each gram of adipose tissue deposited in the body contains about 0.1 gram of water. Thus its caloric yield is 0.9 that of pure fat (9.4 calories times 0.9 equals 8.5 calories).

from the activity of the patient and from the effect of the disease itself (through fever, etc)

To analyze further these figures, the basal requirement was computed from the age, sex, height and average weight, using the charts of Boothby and Sandiford. The energy requirements of these 32 patients, expressed in percentage over and above the basal and classified according to the amount of physical activity and average afternoon temperature throughout the entire hospital stay are given in table 3. This table affords only a rough approximation of the actual energy requirements because of potential errors in the inexact determinations of total caloric intake, body weight, amount of physical activity and mean body temperature, and in the unproved assumption that the weight changes are due entirely to deposition or disappearance of body fat.

TABLE III
Energy Requirements

| Av p m temperature for entire hospital stay | Activity during period of hospitalization | Energy requirement in % above basal calories | | | |
|--|--|---|--------|--------|-------|
| | | 15-30% | 30-45% | 45-60% | Total |
| Normal | Bathroom privileges during less than one-half of period | 6 | 7 | 1 | 14 |
| | Bathroom privileges over more than one-half | 1 | 3 | 0 | 4 |
| | Bathroom privileges during entire stay | 0 | 3 | 0 | 3 |
| 98 ⁸ -99 ⁷ | Bedfast during entire period | 1 | 4 | 2 | 7 |
| | Bathroom privileges for less than one-half | 2 | 1 | 0 | 3 |
| 99 ⁸ -100 ⁷ | | 0 | 0 | 0 | 0 |
| 100 ⁸ -101 ⁶ | Bedfast entire period | 0 | 0 | 1 | 1 |
| | Total | 10 | 18 | 4 | 32 |

For purposes of comparison, the energy requirement of a normal individual under similar conditions may be established from the experimental data of Lusk and others. To cover bodily activity and the specific dynamic action of food, one would expect, from their results, an increment of 15 to 20 per cent in normal individuals confined to bed, of 20 to 30 per cent for bathroom privileges over less than half of the period of hospitalization and of 30 to 45 per cent for bathroom privileges during the greater part or whole of the period. Since the energy requirements of the majority of cases of diabetic tuberculosis fell within the estimated range of normal, it would appear that neither disease uncomplicated by high temperature appreciably

increased the caloric needs of the patient. Similar conclusions for uncomplicated tuberculosis were reached 14 years ago by McCann and Barr.⁷

Composition of the Diet The composition of the diets of each of the 32 patients is given in table 4. The average diet for the entire group contained

TABLE IV
Composition of Diet
(Figures Represent Number of Cases)

| Amt. in grams | 50-74 | 75-99 | 100-124 | 125-149 | 150-174 | 175-199 | 200+ |
|---------------|-------|-------|---------|---------|---------|---------|------|
| Carbohydrate | 1 | 6 | 16 | 6 | 3 | 0 | 0 |
| Protein | 30 | 2 | 0 | 0 | 0 | 0 | 0 |
| Fat | 0 | 0 | 2 | 7 | 13 | 7 | 3 |

108 grams carbohydrate, 62 grams protein, 162 grams fat and 160 grams available glucose.

Protein Thirty patients received from 50 to 70 grams protein daily while two received 75 grams. In terms of average body weight, this amounted to between 0.8 gram and 1 gram per kilo in 20 cases, between 1 and 1.2 gram per kilo in 8 and between 1.2 and 1.35 gram per kilo in 4.

McCann⁸ has pointed out that a diet containing the smallest amount of protein necessary to insure nitrogen equilibrium is desirable in tuberculosis, because the specific dynamic action of such a diet is at a minimum.

Nitrogen balance studies were carried out on two patients for six consecutive days. One was at bed rest with a slightly active lesion and had been receiving 0.8 gram protein and 30 calories per kilo for 10 months, the other was ambulatory with a quiescent lesion and had been receiving 1.1 gram protein and 32 calories per kilo for 13 months. The first patient consumed a total of 58.5 grams nitrogen over a period of six days and excreted a total of 49.5 grams in the urine and feces. The second consumed 68.8 grams and excreted 66.9 grams of nitrogen.* It thus appears that the protein of the diet in both cases was more than sufficient for the bodily needs.

Carbohydrate and Fat The average diabetic diet contained 108 grams carbohydrate and 162 grams fat whereas the average house diet contained between 300 to 350 grams carbohydrate and between 120 to 150 grams fat. Studies are now in progress to determine, if possible, the ideal carbohydrate-fat ratio in diabetic tuberculosis. Though the data are insufficient to permit conclusions, they seem to indicate that a carbohydrate intake of 100 to 125 grams and a fat intake of 150 to 175 grams are about optimal. In this formula sufficient carbohydrate is provided to render the diet palatable and to insure the complete combustion of fat. Since the major portions of the calories come from fat, the pulmonary ventilation is considerably reduced (McCann⁷) with greater rest to the lungs as a consequence.

* Neither patient raised an appreciable quantity of sputum so that nitrogen loss through this source was considered negligible.

Insulin The insulin requirements of each patient are given in table 5. The average amount of insulin needed to bring the patients under control on admission was 46 units daily whereas 42 units were required at discharge.

TABLE V
Insulin Required for Control of Diabetes
(Figures Refer to Number of Cases)

| Units Insulin | 0 | 1-10 | 11-24 | 25-49 | 50-74 | 75+ |
|-------------------------------|---|------|-------|-------|-------|-----|
| At beginning of hospital stay | 3 | 4 | 2 | 6 | 14 | 3 |
| At end | 5 | 2 | 4 | 4 | 13 | 4 |

This does not give a correct impression of the changes in carbohydrate tolerance, since the average discharge diet contained considerably more available glucose than the average admission diet. Correcting for the excess available glucose on the hypothetical basis that 1 unit of insulin is equivalent to 2 grams of glucose, a figure of 34 units daily is obtained as the theoretical insulin requirement at discharge if the admission diet had been carried through.

The total daily insulin at the time of discharge was given in a single injection to four patients, in two doses to six, in three injections to eight, and in four doses to nine. The optimal time for a single daily dose of insulin was 15 to 30 minutes before breakfast, for a second dose, at a similar interval before supper, for a third dose, generally about midnight, and for a fourth dose, before the noon meal. Two patients were encountered who were better controlled when the insulin was given after meals.

DIABETIC MANAGEMENT AT THE TIME OF SURGICAL TREATMENT OF THE TUBERCULOSIS

Pneumothorax was induced in 22 of this group, phrenic surgery was performed in 18, pneumolysis and thoracoplasty in one each.*

Pneumothorax and phrenic operations were performed by the thoracic surgeon whenever indicated without consulting the physician in charge of the diabetes. Hyperglycemia and glycosuria often occurred on the day of the operation, but quickly disappeared unless a pleural effusion developed or secondary infection occurred.

Before each stage of the thoracoplasty was attempted, however, the diabetes was carefully controlled. Three hours before the operation was scheduled, the usual morning dose of insulin was given, together with the glucose equivalent of breakfast in some readily assimilable form (such as sweetened orange juice). As soon as the patient returned from the operation

* Thoracoplasty has been successfully performed in another diabetic not included in this group of 32.

ing room, a urine specimen was obtained and analyzed for glucose. Insulin was then given subcutaneously in accordance with the results of the Benedict test, 20 to 25 units, if orange, 15 to 20, if yellow, 10 units, if green, 5 units, if blue. This was followed by the intravenous injection of 25 grams glucose in 250 to 500 c c saline. This procedure was repeated every four hours around the clock until the patient was able to take nourishment by mouth, when feedings containing a similar amount of available glucose were substituted for the intravenous glucose. After two or three days, provided the diabetes was under control, the patient was placed upon his preoperative dietary formula, divided into three or four highly concentrated feedings.

RESULTS

Outcome of Tuberculosis The results to date in the entire group of 80 cases, classified according to the criteria adopted by the National Tuberculosis Association have been discussed at length elsewhere.⁴ At this time we will merely set down, in brief, the results in the 32 cases on which the nutritional studies have been based. Twenty-seven of the cases were classed as far advanced on admission and five as moderately advanced.

On April 1, 1934, seven of the group were dead, one was untraced and 24 were known to be alive. Nine of the latter were classed as arrested or apparently arrested, four as quiescent, four as improved and seven as unimproved. The deaths were all due to tuberculosis. None of those who died in the hospital showed a clinical degree of acidosis at death. Three moribund patients, not included among this group of 32, died during insulin reactions. In each instance it was felt that the reaction probably precipitated a death that was inevitable. Severe insulin reactions occurred in many whose strength was slightly or moderately impaired without threatening life.

Carbohydrate Tolerance The available glucose in the diet in excess of the insulin required to keep the blood sugar below 140, calculated on the basis that 2 grams glucose are covered by 1 unit of insulin, may serve as an index of carbohydrate tolerance. Though this method is necessarily inaccurate, due to the fact that the insulin glucose equivalent varies within rather wide limits, it still furnishes a rough measure for evaluating improvement or retrogression in the diabetes. The glucose uncovered by insulin when the diabetes was first brought under control and again at discharge is given in table 6.

TABLE VI

Available Glucose in Diet in Excess of Insulin
(Calculated on Basis that 1 Unit of Insulin Is Equivalent to 2 Grams Glucose)

| Grams glucose | -50 to 0 | 1-49 | 50-99 | 100-149 | 150-199 | 200+ |
|-------------------------------|-------------|------|-------|---------|---------|------|
| At beginning of hospital stay | 4 | 11 | 9 | 8 | 0 | 0 |
| At end | 3 | 11 | 5 | 8 | 3 | 2 |

The carbohydrate tolerance was regarded as markedly improved when there was an increase of more than 50 grams in the available glucose uncovered by insulin, slightly improved when there was an increase of from 15 to 49 grams, and unchanged when there was an increase or decrease of less than 15 grams. A decrease of from 15 to 49 grams was considered a slight fall in carbohydrate tolerance, a decrease of more than 50 grams, a marked fall. According to these criteria, the carbohydrate tolerance showed a marked improvement during the period of hospitalization in 11 cases, a slight improvement in four, no change in seven, a slight fall in four and a marked fall in six.

Effect of Tuberculosis upon Carbohydrate Tolerance Twelve patients had been under observation in diabetic clinics prior to the onset of the tuberculosis*. Five of these showed a marked fall in tolerance with the advent of the tuberculosis, five showed a slight fall and two showed no appreciable change.

The effect of the tuberculosis upon the diabetes during hospitalization is given in table 7. The carbohydrate tolerance was determined in the manner described above at the beginning and end of a period in which there

TABLE VII
Effect of Tuberculosis on Carbohydrate Tolerance

| | Carbohydrate Tolerance | | | | | | Total |
|--------------|------------------------|----------------------------------|---------------------------------|------------------------------|------------------------------|---------------------------|-------|
| | | Markedly Improved +50 or more | Slightly Improved +15 to +49 | Un- changed +14 to -14 | Slightly Worse -15 to -49 | Much Worse -50 or over | |
| TUBERCULOSIS | Considerably improved | 7 | 0 | 0 | 0 | 3 | 10 |
| | Slightly improved | 4 | 6 | 4 | 3 | 0 | 17 |
| | Slightly worse | 2 | 1 | 3 | 4 | 4 | 14 |
| | Much worse | 3 | 1 | 3 | 1 | 1 | 9 |
| | Total | 16 | 8 | 10 | 8 | 8 | 50 |

was a definite change, both in serial roentgen-rays and in constitutional symptoms. Several patients showed periods of improvement and retrogression in the tuberculosis and consequently are represented more than once in the table. It does not necessarily follow, of course, that the change in tuberculosis was responsible for the change in carbohydrate tolerance merely because the two were coincidental. However, care was taken to eliminate from consideration any period in which there was an obvious cause for

* We wish to acknowledge our indebtedness to Dr. F. B. Peck for his permission to use the Grace Hospital diabetic records.

the change in tolerance apart from the tuberculosis (for example intercurrent pyogenic infection, etc.) It is, of course, impossible to eliminate spontaneous fluctuations in tolerance independent of the tuberculosis.

In 27 instances, there was a parallel change in the tuberculosis and diabetes, in 17 cases, both showed improvement concurrently, in 10 cases, both became worse. In 13 instances the courses of the tuberculosis and diabetes were divergent. An improvement in tuberculosis was accompanied by a fall in carbohydrate tolerance in six cases, whereas the reverse occurred in seven.

Thus there appears to be no fixed rule governing the effect of tuberculosis upon coexistent diabetes. The courses of the two diseases are usually parallel but may be divergent.

An intercurrent pleural effusion, however, is generally accompanied by a temporary fall in tolerance. A marked fall in tolerance occurred coincidentally with the development of an effusion in three cases, a slight fall in six, no appreciable change in three and a slight rise in only one.

SUMMARY AND CONCLUSIONS

1 This study is based upon a group of 32 patients with coexisting diabetes and tuberculosis, each of whom was in the hospital for six or more consecutive months, the average length of stay being 555 days.

2 The composition of the average diet for the entire group was as follows: carbohydrate 108 grams, protein 62 grams, fat 162 grams, available glucose 160 grams, total calories daily 2138. In comparison, the average house diet contained 2500 to 3000 calories apportioned as follows: 300 to 350 grams carbohydrate, 80 to 85 grams protein and 120 to 150 grams fat. Owing to its relatively higher fat and lower protein and carbohydrate content, the diabetic diet is theoretically more suited to the treatment of tuberculosis since less energy is dissipated in the digestion and assimilation of food and less pulmonary ventilation is required.

3 This diet furnished an average of 34 calories per kilo and was sufficient to permit an average weight gain of 7.4 kilos (16¼ lbs.). The energy requirements, calculated in percentage over and above the basal, fell within the estimated range of normal in the majority of cases of diabetic tuberculosis. It would thus appear that neither disease appreciably increased the caloric needs of the patient.

4 Nitrogen balance studies were done on two patients receiving 0.8 gram and 1.1 grams protein per kilo respectively. Both were in positive balance at the time of the studies.

5 The average amount of insulin required to control the diabetes was 46 units daily on admission and 42 units daily at discharge. There was a marked improvement in carbohydrate tolerance during the period of hospitalization in 11 cases, a slight improvement in four, no change in seven, a slight fall in four and a marked fall in six.

6 The tuberculosis was classed on admission as moderately advanced in five cases, and as far advanced in 27. Pneumothorax was induced in 22 of the group, phrenic surgery was performed in 18 and thoracoplasty in one. On April 1, 1934, seven of the group were dead, one was untraced and 24 were alive. Nine of the latter were classed as arrested or apparently arrested, four as quiescent, four as improved and seven as unimproved.

7 The course of the tuberculosis and diabetes was parallel in 67 per cent of the cases, in 42 per cent there was concurrent improvement in both diseases, and in 25 per cent concurrent retrogression. An improvement in tuberculosis was accompanied by a fall in carbohydrate tolerance in 15 per cent whereas the reverse occurred in 18 per cent. An intercurrent pleural effusion was generally accompanied by a temporary fall in tolerance.

Acknowledgment of our indebtedness is made to Dr. Samuel S. Altshuler for his aid in diabetic management, to the Superintendent of Herman Kiefer Hospital, Mr. George Phillips, and to the medical, surgical and dietetic staffs of the Tuberculosis Unit for their splendid cooperation.

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ERYTHREMIA¹

By LOUIS FAUGERES BISHOP, M D, F A C P, LOUIS FAUGERES BISHOP, JR, M D, F A C P, and MAX TRUBEK, M D, *New York*

THE clinical recognition of erythremia should no longer offer difficulty. Its essential features have been identified by Vaquez,¹ and the clinical syndrome made familiar since the descriptions by Osler^{2,3}. The finding of an enlarged spleen in a patient with generalized "red" cyanosis should bring to mind the diagnosis of erythremia. More commonly, splenomegaly is associated with diseases characterized by anemia. The clinical distinction of polycythemia vera becomes difficult when we see the occasional patient suffering from this disease who presents himself in the late stages with anemia⁴ rather than polycythemia. The correct interpretation can then usually be made from the past history. Congenital heart disease at times produces a similar picture aside from the cardiopathy. We have recently encountered such a patient who exhibited an enlarged spleen in addition to a polycythemic blood picture. Where cyanosis and an increased red blood count are the result of pathologic changes in the lungs or pulmonary vessels, splenomegaly is, as a rule, not present and the respiratory symptoms help to identify the pathologic picture. When cyanosis is the result of mediastinal pressure due to new growth (lymphoblastoma) and there is concomitant involvement of the spleen with enlargement, the absence of an increased blood count differentiates the condition. In such cases the cyanosis is not generalized and not "red."

The case to be presented was observed between the years 1927 and 1932, and an opportunity was afforded to study the patient both clinically and pathologically. An episode of colonic bleeding and diarrhea, diagnosed as amebic colitis, was of particular interest because of its effect upon the blood counts.

CASE REPORT

I B D D, white, male, aged 65 years, occupation—civil engineer, had been employed in the tropics over long periods of time. He consulted us in 1927 complaining of substernal distress after meals. He had recently been told that he was suffering from an abnormal blood condition. There was no family history of other members suffering from this disease. He had had typhoid at the age of twenty-eight. In 1926 he had the first symptoms which led to the diagnosis of amebic dysentery.

On physical examination he presented the findings classical for erythremia: cyanosis, splenomegaly and polycythemia. The spleen was hard and smooth. The rounded edge was felt about four inches below the costal margin. The liver edge was at the costal margin. The blood pressure was 140 mm Hg systolic and 90 mm Hg diastolic. The Wassermann reaction on the blood serum was negative. The electrocardiogram showed widening of the QRS complexes in all three leads, with an inverted T-wave in the first lead. The urine contained a heavy trace of albumin.

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and showed 10 to 15 red blood cells per high power field. The blood counts are summarized in table 1, and the laboratory proceedings enumerated in table 2. A roentgen-ray of the colon after a barium enema revealed the displacement of that organ by the enlarged spleen.

TABLE I*

Blood Studies

| Date | R B C | W B C | Hemoglobin | Platelets |
|------------|-----------|--------|------------|-----------|
| 3/27/1927 | 6,000,000 | 18,000 | 100% | |
| 11/7/1927 | 7,552,000 | 15,600 | 110% | |
| 1/14/1928 | 8,640,000 | 10,200 | 105% | |
| 2/12/1929 | 4,120,000 | 10,000 | 85% | |
| 6/12/1929 | 4,400,000 | 10,750 | 81% | |
| 11/26/1930 | 7,960,000 | 30,700 | 126% | 210,000 |
| 1/27/1931 | 8,860,000 | 25,750 | 130% | |
| 2/17/1932 | 9,050,000 | 18,550 | 136% | |
| 7/3/1932 | 7,980,000 | 12,720 | 135% | |

* The blood counts were always elevated except during 1929, the lowered counts coinciding with the episode of colonic bleeding. In the differential count the polynuclear cells averaged about 90 per cent, there were no other variations from normal. No immature red cells or pathologic white cells were ever identified in the smears. The platelets appeared definitely diminished in numbers in proportion to the red cells, occurring singly or in small clumps with occasional giant forms.

TABLE II*

Laboratory Data

| | |
|-------------------------------|--|
| Bleeding time | 7 minutes |
| Coagulation time | 12 minutes (tube method) |
| Clot retraction | Firm after 6 hours with good separation of serum |
| Volume index | 1.02 |
| Blood serum calcium | 16 mg per 100 c c |
| Proportion of cells to plasma | Red cells Plasma |
| | 80% 20% |
| Red cell fragility test | Hemolysis began 48% saline |
| | Hemolysis complete 32% saline |
| Basal metabolism | Plus 49 |

* The important variations from normal were the increased basal metabolism and increased calcium, characteristic alterations in this disease. The proportion of red cells was markedly increased over their normal relation to plasma (48/52). The blood sugar and blood nitrogen elements were always within relatively normal limits, except for a terminal non-protein nitrogen of 70 mg per cent.

The year 1927 was uneventful except for some mild arthritic pain in his right knee. He made a trip to Nicaragua and when he returned in 1928 his diarrhea became much more marked. It was not, however, bloody. *Entameba histolytica*, both the encysted forms and motile protozoa, were found in his stools on several occasions—February 7 and March 6, 1928—and treatment was begun for amebiasis. This consisted of several courses of emetine hydrochloride, bismuth, yatren, and a careful diet. After several months these symptoms disappeared and did not recur. The stools were subsequently negative for entamebae.

In November 1930, after returning from South America, he reported several new episodes in the course of his disease. He had had several attacks of hematuria during the preceding August and had been advised to have roentgen-ray treatment. At that time his right knee and his great right toe had become swollen and tender. He now also complained of cramps in his legs at night.

On February 23, 1931, he had a profuse pulmonary hemorrhage following which

he was in shock. He responded well to morphine. It was then decided to give him some roentgen-ray treatment to his long bones and for this purpose he was referred to Dr Leon T Le Wald.

Small doses of roentgen-ray therapy were given over the long bones, using moderate voltage (120,000 K V), filtered through 4 mm of aluminum at a 40 cm distance, using from 50 to 100 milliamperes minutes, repeated at intervals of from 3 to 14 days, between February 28 and July 14, 1931. Treatment was also administered to the spleen between April 21 and July 14, 1931, and one treatment to the liver was given on July 14, 1931. Treatment was given again to the long bones between March 8 and April 14, 1932, and one treatment to the spleen on March 14, and another on March 26, 1932, and one treatment to the liver on March 31, 1932.

On April 6, he again complained of pain in his feet and ankles and was relieved somewhat by aspirin and atophan. At this time he noted that he could mentally concentrate better and that he could do things that had previously been an effort. We felt that there was at least some clinical improvement from the roentgen-ray treatment he had received. On April 22, he developed a tender purpuric spot over the right hip, apparently a hemorrhage. In May again he complained of arthritis. Unsuccessful attempts were made to relieve this by removal of foci of infection, such as a bad tooth and washings of the sinuses.

He went along very well until April 29, 1932. His blood count was unchanged (table 1), and there were no symptoms resulting from his polycythemia. All this time he was receiving roentgen-ray treatment to his long bones, liver and spleen. During this period he developed pitting edema of his ankles and it was noted that there was a definite increase in the size of his heart after comparing the transverse diameter measurements with the previous ones.

On May 16, 1932, the following observations were made. The edema had increased, there were many moist rales at the lung bases and the liver was enlarged and tender. He was ordered to bed and treatment for congestive heart failure was instituted. From this point on his course was progressively downward, he gradually developed generalized anasarca. The response to mercurial diuretics was not satisfactory and he developed a toxic diarrhea from the mercury. On July 19, he developed a unilateral eruption (herpes zoster) over his lower back which gradually became generalized in distribution and hemorrhagic in nature. His terminal symptoms were uremic, there were muscular twitchings and delirium. The non-protein nitrogen of the blood was found to be 70 mg per cent. The urine sediment contained many hyaline and a few finely granular casts and white blood cells. On July 27, he went into coma and died on July 28, 1932.

AUTOPSY FINDINGS

There was marked edema of the soft tissues of the back and flanks. There was considerable pitting edema of the lower extremities and of the fore-arms and hands. The pleural cavities were free of adhesions and each contained about 1500 cc of clear amber fluid. The lungs were edematous. The heart weighed 450 grams. Both the left and right coronary arteries traced through their finer ramifications showed widely patent lumina. The vessel walls were free of any change and cross-sections of the finer twigs showed no visible occlusion anywhere. The intima of the aorta showed only small superficial yellow streaks of early atherosclerosis.

The peritoneal surfaces were glistening, the cavity contained about 1500 cc of dark fluid. The mucous membranes of the proximal ileum and of the jejunum were intensely red and contained light red fluid. Careful search for mucous membrane lesions or serosal induration was unsuccessful. The colon in its proximal half contained a small amount of yellowish fecal material, the distal half was empty. Similar search of residual or recent mucous membrane or serosal lesions was likewise

without success. The mucosa was intensely red, for the most part, and the serosa everywhere glistening.

The liver weighed 1500 grams and on section showed early "nutmeg" appearance. There were no abscesses. The surface was smooth and not thickened. The spleen was in a vertical position in the lateral aspect of the abdominal cavity. Its lower border was about 4 inches below the costal margin. The weight of the organ was 740 grams. There was a prominent notch in the normal position along the mesial border. On the upper surface there was a large irregular area of capsular wrinkling and thickening of a light brown color in contrast to the purple splenic capsule. There was a smaller area of similar capsular thickening and wrinkling at the medial anterior surface. Section of the spleen showed a firm, intensely red parenchyma, without any oozing of blood, homogeneous and without visible lymphoid follicles. Beneath the areas of capsular thickenings the parenchyma was lighter in color and indurated so that it was demarcated from the rest of the pulp and visible as circumscribed areas, each about 2 inches in diameter (figure 1). There was no

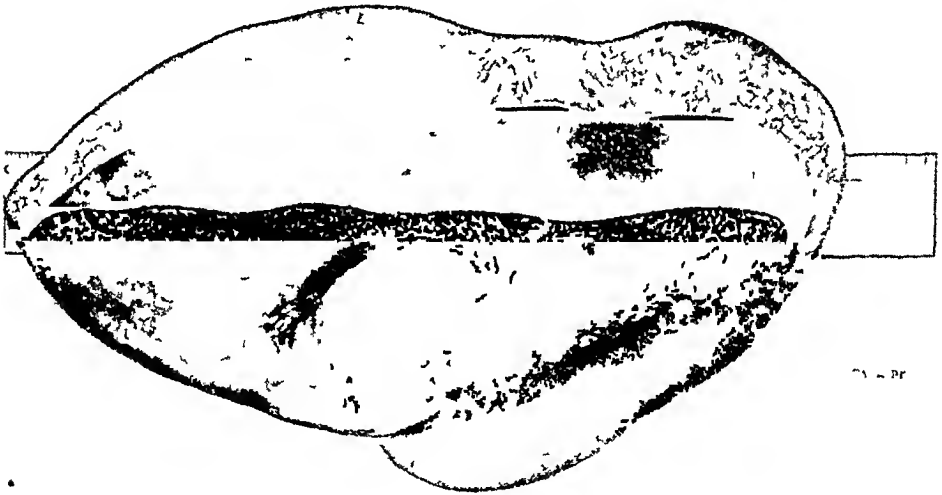


FIG 1 The spleen was enlarged and firm. On section the parenchyma was deep red and homogeneous except for two circumscribed areas, lighter in color, situated beneath corresponding areas of capsular wrinkling and thickening.

accessory spleen. The splenic vein was followed from the hilus into the portal vein and the mesenteric veins were opened. All of these vessels were free from disease and thrombi. The splenic artery was entirely normal, its lumen was unusually large for this vessel and showed no arteriosclerosis. There were no enlarged peri-portal nodes. The kidneys were very unequal in size, the left weighed 450 grams, the right 30 grams. The capsule of the left kidney was free, its surface was diffusely, finely and coarsely granular, with a few small cysts containing clear fluid. The parenchyma was deep red and firm, the cortex was remarkably narrowed and irregular and its relations to the medulla were about one to three and one-half, measuring three to four mm. in width. The right kidney was similarly granular.

Bone Marrow Cross-section of all the ribs which were examined showed abundant deep red marrow, with a thin cortex, the middle of the sternum was likewise distended with deep red soft marrow (figure 2). The entire marrow cavity of the lower end of the right femur was filled with deep red soft substance which occupied

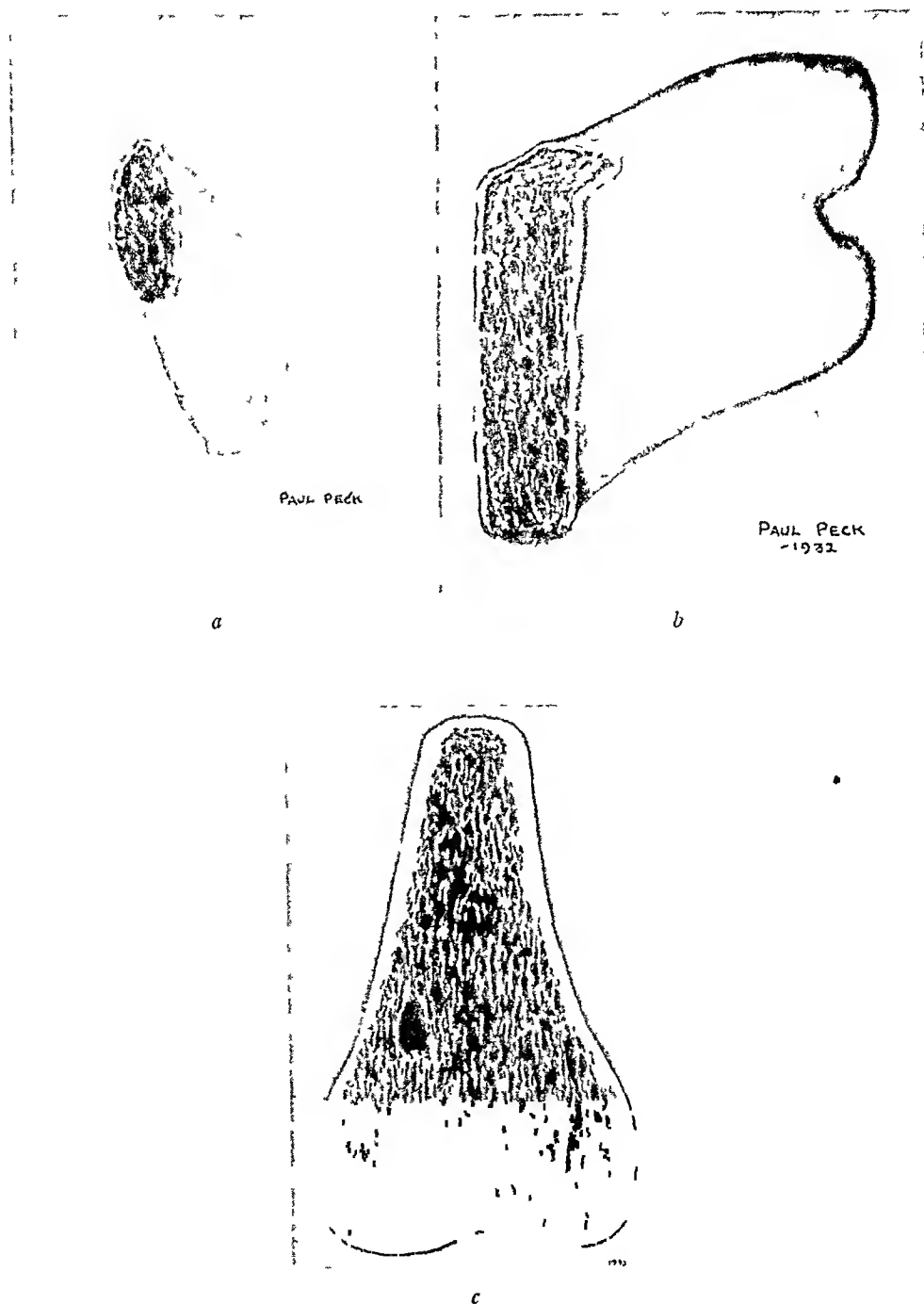


FIG 2 Section of all the ribs (a) showed abundant, deep red marrow with a thin cortex. The sternum (b) was likewise distended with deep red soft marrow. The lower end of the right femur (c) showed a similar marrow. There was an increase in the bony trabeculations, the cortex was thinner than normal.

even the epiphyseal end of the bone down to the cortex of the articulating surface of the knee. The cortex of the bone appeared normal except for perhaps slight thinning. There was an increase in the bony trabeculations of the marrow (figure 2 c). The right knee joint was distended with about 150 cc of clear, thin yellow liquid.

Microscopically, sections of the spleen through the indurated areas beneath the region of capsular scarring showed a moderate thickening of the fibrous trabeculae of the pulp with propagated fibroblastic tissue extending out into the parenchyma so as to considerably diminish the size of the vascular spaces as compared with the less dense portions of the organ. The arterioles of the follicles were markedly thick walled and only in isolated instances showed any residuum of the normal lymphocytic mantle. The parenchyma appeared moderately cellular. With oil immersion magnification there was seen, in addition to the large endothelial cells lining the blood channels of the pulp, elongated reticulo-endothelial cells, and large and small accumulations of developing blood cells among which could be identified nucleated red cells, mature polymorphonuclear cells and immature large mononuclear white blood cells. These cells were in all instances interspersed with red blood cells so that it was difficult to decide the relationship of such blood cell islets to the vascular channels and pulp spaces. These cellular accumulations were, more often, particularly dense about the fibrous trabeculae. The striking difference seen in sections through the softer hemorrhagic portions of the organ was the more marked distention of the sinuses with closely packed red cells and far less interstitial fibroblastic tissue and relatively few white cells.

The kidneys in some areas showed widespread disease of the arterioles characterized by subendothelial fibroblastic proliferation often approaching and at times resulting in complete obliteration of the lumina. Almost all of the glomerular tufts in these areas showed changes, varying from a slight degree of peri-capsular fibrous thickening to marked encroachment on the substance of the glomerulus. Some were completely fibrotic, others had gone on to hyalinization. The large arteries were relatively normal.

Sections of bone marrow from rib, lower end of sternum and lower end of right femur showed essentially similar types and distribution of cells in each of these areas. The marrow of the rib appeared the least cellular, while that of the femur was the most richly cellular of the areas studied. Almost no residual fatty areas were found. The cellular elements, for the most part, could be separated into two major groups in nearly equal distribution as to numbers (figure 3). These represented the erythroblastic and myeloblastic series. In addition there was a generous number of scattered multinucleated giant cells, the megakaryocytes, as well as of the elongated cells of the reticulo-endothelium, and a large number of mature red blood cells. The normoblasts were identified by their small, round deeply staining nuclei with a pale cytoplasmic rim, many nuclei were in the process of budding, some were large with scalloped outline and others showed small satellite nuclei. The cells of the myeloblastic series were chiefly large, non-granular premature stem cells. The nuclei were granular, varied in size, at times occupied nearly all of the cell, in other instances smaller, with a rim of faintly pink staining cytoplasm. A considerable number of eosinophilic myelocytes could be easily identified. Only rarely was there seen a metamyelocyte or a segmented polynuclear cell.

DISCUSSION

We did not consider the use of phenylhydrazine advisable in our patient because of his age, and the diseased kidneys discovered at autopsy justified our decision. The roentgen-ray therapy produced little improvement in his blood counts, although subjectively he was somewhat benefited. The

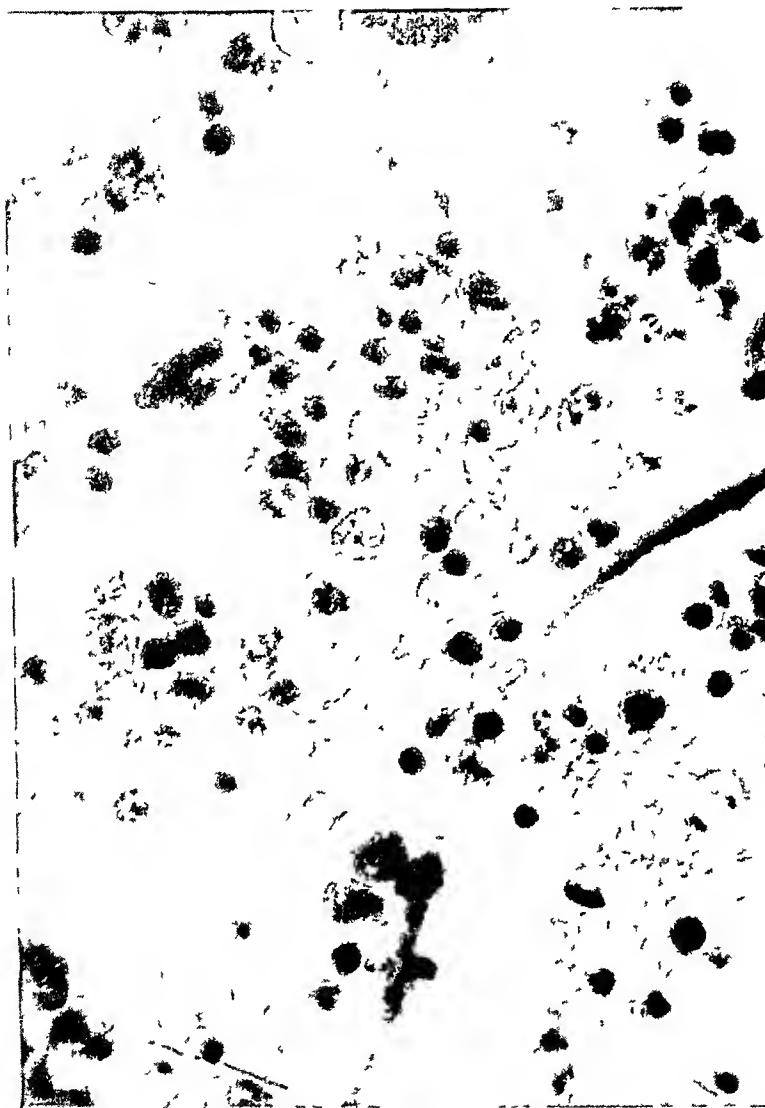


FIG 3 Microscopic section of sternal marrow, Giemsa stain. The cellular elements represent the erythroblastic and myeloblastic series, in nearly equal distribution. The normoblasts are identified by their small, deeply staining nuclei with a pale cytoplasmic ring. Some are in process of budding, some have large nuclei with scalloped outlines, others show small satellite nuclei. There are a large number of mature red blood cells. The cells of the myeloblastic series are chiefly large, non-granular stem cells. A considerable number of eosinophilic myelocytes were identified. A generous, though not excessive, number of megakaryocytes were found, one is noted at the upper margin of the photograph.

colonic bleeding resulting from his amebiasis seemed to effect a distinct lowering of his red blood cell counts. Ordinarily, frequent venesections do not ameliorate this condition. The identification of the *Entameba histolytica* had been confirmed by a competent protozoologist. The response to specific therapy was prompt. After death we had the unusual opportunity of examining the bowel of the patient cured of amebiasis. The complete absence of pathologic residua in such a case, both on gross and microscopic examination of the organs, is not a surprising finding according to experienced workers in this disease.⁵

The gross and histologic findings of generalized and active hematopoiesis did not impress us as having the morphology of a neoplasm of the blood-forming elements, as Minot⁶ has suggested. There were no extramedullary foci of blood formation except for the myeloid alterations of the spleen. The lymph nodes were not enlarged. The microscopic sections showed all the normal elements of blood formation in equal and active regeneration. The bone marrow response was much as we see in active hematopoietic stimulation, not unlike that produced by bone marrow metastases of carcinoma of the prostate. In this case the stimulus remains unknown.

The hypercalcemia did not result in any unusual degree of atherosclerosis. The enlarged heart was evidently not necessarily due to the polycythemia since the nephrosclerosis with hypertension might equally well have been the cause. The heart showed no alteration except for hypertrophy. The coronary arteries, carefully examined, were not diseased. The precordial distress and the electrocardiographic changes must be ascribed to the hypertrophy of the myocardium. Death was apparently due to congestive heart failure with concomitant uremia. There were no terminal thromboses or hemorrhages, such as often cause death in erythremia. The use of salyrgan, indicated by the large accumulations of fluid and edema, probably hastened failure of the already markedly damaged kidneys.

The increased basal metabolism probably goes along with active regeneration of blood, such as we see in leukemia to a more marked degree. The blood was viscid and the proportion of red blood cells to blood plasma was markedly increased. The enlarged spleen was characteristic, except that it was more firm than is usual, probably the result of the roentgen-ray therapy, which may also account for the scarred areas in this organ. The splenomegaly was to some extent explained by the myeloid metaplasia, but for the most part was due to the great increase in blood content. We have seen a case where the enlarged spleen rapidly decreased in size just before death due to a fatal gastrointestinal hemorrhage, demonstrating the reason for the enlarged organ in that patient with polycythemia vera.

The nationality of our patient was American of English ancestry, therefore, not conforming to the majority of patients with erythremia who as Dr. Paul Reznikoff⁷ has shown from the series he compiled, more usu-

ally come from Eastern Europe This author also pointed out the presence of arteriosclerosis in the smaller arteries in the bone marrow sections of our case and considered it a finding of considerable significance If these vascular changes were the cause of a relative anoxemia of the bone marrow this might be an etiologic factor of importance

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THE TREATMENT OF LOBAR PNEUMONIA BY ARTIFICIAL PNEUMOTHORAX

A STUDY OF TWENTY-FIVE CASES

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THE correct appraisal of a new therapeutic measure is always difficult and in a disease presenting as many variables as pneumonia, it is particularly so. Not only does the mortality vary in different years but it is influenced by the age of the patient, the type of pneumococcus, the presence of complications and especially by the duration of the disease before the treatment is begun. Accordingly, no final opinion as to the value of any treatment can be arrived at until a large group of treated cases is compared with a similar untreated group. Our series is so small that no definite conclusions can be drawn, we merely present our observations together with certain impressions we have received.

While a number of clinicians in several widely separated parts of the world had reported successful results with this treatment,¹ it was not until the work of Lieberman and Leopold² who treated experimental pneumonia by pneumothorax, that a real interest in the procedure developed. Of the 18 dogs in their series not given treatment, 13 died, of the 18 treated, three died. They were able to find only 50 human cases reported—the ages varying from six weeks to 62 years. In some of these the benefits of the treatment were not especially convincing though the relief of pain was noted by all. Since their paper, 11 cases have been reported by Behrend and Cowper,³ and Blake⁴ had also reported a group of 24 cases.

RATIONALE OF TREATMENT

Before proceeding to review our results or to discuss certain controversial points, let us consider the rationale of the procedure.

When one thinks of the pathology of lobar pneumonia he is apt to visualize the consolidated lung as seen at autopsy five or more days after the onset, and the futility of trying to collapse or even compress so solid an organ is very apparent. This, however, is a terminal stage and is as different from the condition present during the first few hours after onset as the ruptured, gangrenous appendix differs from the slightly injected organ that characterizes the early stage of this disease.

Terrell, Robertson and Coggeshall⁵ produced experimental lobar pneu-

* Received for publication April 17, 1935.

From the Medical and Roentgenological Services of Hartford Hospital.

monia in dogs by introducing virulent culture into a terminal bronchus. They found that the earliest and most striking finding was extensive perivascular edema. Many of the alveoli also were filled with fluid. While these changes were evident as early as the first hour, they were not marked until the sixth hour, and by the twelfth hour the greater part of the lobe was consolidated and fibrin was beginning to form on the pleura. The most recently involved part (the periphery) was the most moist, the central or older part, less so, and an observation of the greatest significance was that pneumococci were most numerous in the periphery of the lesion, i.e. where the edema was greatest.

Inasmuch as Rhoads and Goodner⁹ believe that edema fluid is the principal agent in the dispersion of pneumococci, any measure that has as its object the mechanical limitation and dissipation of the congestion and edema, must be given attention. According to Lloyd,¹² by increasing the intrapleural pressure in a pneumothorax, the lymph flow may be reduced by as much as 50 per cent.

In studying the blood flow through the lungs after experimental pneumothorax in rabbits, Dock and Harrison⁷ found that even though they employed slightly positive pressure, complete atelectasis of the collapsed lung did not occur at once. Only when positive pressure was maintained for from three to five days did a complete atelectasis result. They concluded that the therapeutic value of artificial pneumothorax must be ascribed to ischemia.

Fifty years ago when Foralini began to treat tuberculosis with pneumothorax, he felt that a complete collapse of the whole lung was desirable. As experience accumulated, it became evident that this extreme measure had very definite disadvantages, and finally the idea of partial or selective compression found acceptance among phthisiotherapists. Selective collapse is in effect "an automatic mechanism, the resultant action of the simultaneous tendency of the diseased part to collapse and of the healthy part to expand."⁸

The act of coughing suddenly raises the intrapleural pressure and a mean pressure that on quiet breathing is zero, or even slightly negative will suddenly become strongly positive with sharp cough. For this reason, during the pneumothorax treatment of pneumonia, complete abolition of cough is perhaps undesirable. Lobar pneumonia and subacute, or chronic tuberculosis, differ so much in their pathology and course that the rather leisurely compression of the tuberculous lung generally practiced would not be applicable to the more acute disease.

Can one secure selective compression or collapse of a lung which is the site of a beginning pneumonia? This is hard to determine because the patient, as a rule, is so ill that it is difficult to obtain satisfactory serial roentgen-ray films. We were fortunate, however, in having an early patient who, because he did not seem very ill, was given only one injection of 250 c.c. about 30 hours after the onset, for the relief of pain. Figure 1 shows

the lesion at the right base on admission. Figure 2, which was taken about 20 hours after the air injection, shows the lung to be adherent in the lower axillary region but separated from the diaphragm elsewhere by air. There is also a small amount of air at the apex. Most of the air, as the lateral view showed, lay between the lesion and the anterior chest wall. The chief interest, however, is the fact that the pneumonic area shows considerable clearing due presumably to the lessening of the edema and congestion as the result of the selective collapse. Furthermore, the immediate relief of pain that so often follows the injection of a very small amount



FIG 1



FIG 2

Selective collapse following single injection of air in early lobar pneumonia

FIG 1 Right lower lobe, second day of disease before treatment

FIG 2 After injection of 250 cc air. Small amount of air at extreme apex, slight separation of lower lobe from diaphragm by air. (In the lateral view considerable air was seen anteriorly.) Note especially that the right lower lobe is much better aerated due presumably to less congestion and edema. (In the diagrams accompanying roentgen-rays, normal lung is left blank, pneumonic areas are dotted and pneumothorax is entirely black.)

of air (50 to 100 cc) can be accomplished, obviously, only by compressing the lung at the site of the lesion.

Autopsy proof that a small amount of air can cause a selective compression of a lobe, the site of an influenzal pneumonia, was furnished in 1918 by Rood⁹ while doing lung punctures on a number of patients ill with influenzal pneumonia to determine if possible the infecting organism. A few developed pneumothorax as a result. As they seemed to be much improved when this occurred, he injected three apparently moribund pa-

tients with from 100 to 150 cc of air. Two recovered and the third showed striking improvement but relapsed and died. At the autopsy the lower lobe the site of the pneumonia, was compressed to one-third of its normal size and did not contain the usual amount of exudate, while the upper lobe, which was not hemorrhagic, showed but little compression. It is of interest that such a small amount of air was able to produce so marked a selective collapse of the pneumonic lobe.

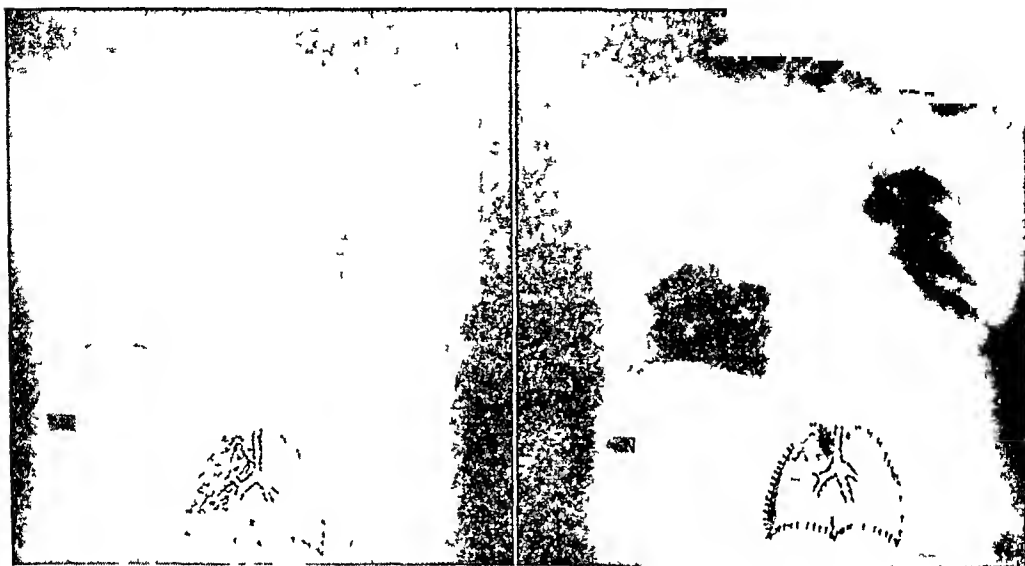


FIG 3

FIG 3 Consolidation right upper, third day

FIG 4 After 650 cc of air

FIG 4

ANALYSIS OF CASES

At the beginning of our investigation it was appreciated that if only such patients were treated as had not been ill over three days, and if the elderly cases with complications were excluded, a much lower mortality would be obtained. Such a selection should be made if a control group of non-treated cases could be run at the same time. As this was not possible with the material available, it was decided to treat all cases as they came in. This was done with the exception that two very mild cases were not given injections as we felt they would recover without any treatment. No case was admitted in extremis. All patients on admission had a blood culture, a leukocyte count and a bedside roentgen-ray (both postero-anterior and lateral). The treatments were followed by frequent roentgen-rays, from 10 to 15 being taken in many cases. This work was under the supervision of Dr. Ralph T. Ogden.

Of the 25 patients, seven died—a mortality of 28 per cent. Felton's

antipneumonic serum was administered to three who died and to an equal number of those who recovered. In two of the fatal cases it was used too late to be of value.

Fatal Cases In the main, the fatal cases (table 1) were elderly indi-

TABLE I *

Fatal Cases

| H II Num- ber | Age Sex | Type Site | Days Dis | Bld Cult | No. Treat Total Amt | Relief Pain | Prompt Detoxi- fication | Day Death | Days Serm Given | Complications Comments |
|---------------------|------------|---------------------|-------------|-------------|---------------------------------|----------------------|-------------------------------|--------------|-----------------------|---|
| 287680 S I | 69 M | II R u | 4 | + | 5 1500 c c | No | No | 7 | No | Adhesions +3 Severe asthma |
| 287737 O W | 75 F | I R l | 2 | + | 6 2125 c c | No | No | 4 | 3 30 000 units | Adhesions +3 Severe asthma Empyema (Pneumo) |
| 287796 I P | 53 M | I L l R u m | 5 | + | 2 1250 c c | Pain incr ad h | No | 7 | 6 51 000 units | Auric fibril Arteriosclerosis Adhesions +3 (N P N 89) Serous effusion |
| 289058 A W | 85 F | III R u | 4 | + | 3 475 c c | +3 | No | 5 | No | Coronary thrombosis |
| 288023 I S | 50 M | IV R u m | 3 | + | 3 1850 c c | +3 | 2 | 7 | No | Diabetes—Peritonitis (?) Large intest hemorrhage |
| 288583 C F | 30 M | I L l | 3 | — | 4 800 c c | +1 | 2 | 14 | 6 90 000 units | Adhesions +3 Empyema (Pneumo) Peritonitis, intest obstr (<i>B. coli</i> , few non hemolytic strep) |
| 287482 J A | 71 F | III L l R u m | 6(?)* | — | 12 5L 900 c c 7R 1625 c c | — | No | 13 | No | Adhesions +2 Nephritis (N P N 150) |

* Estimating the day of disease when pneumonia follows a "cold" is often very difficult. History frequently suggests an older lesion than physical signs or roentgen-rays indicate.

In tables 1, 2 and 3 R is right lung

L " left lung

u " upper lobe

m " middle lobe

l " lower lobe

In the tables, the degree of relief of pain and detoxication is expressed numerically, 3 indicating marked, 2 and 1 less so.

Adhesions 4 No pleural space

3 Preventing collapse of pneumonic area

2 and 1 Strings or bands that allow some compression of the involved lobe

viduals with a variety of severe complications who had been ill several days when treated. Extensive adhesions prevented satisfactory compression of the lung in practically all cases. The average age of the fatal group was 62 years. Only one was under 50, three were over 70 and one 85. Of those who recovered, the average age was 25 years. The patients who died had been ill on an average of 3.8 days when treated, those who recov-

TABLE II

| No. cases | Age | Deaths |
|-----------|--------------|--------|
| 5 | under 20 yrs | None |
| 7 | 20-39 " | 1 |
| 8 | 40-59 " | 2 |
| 5 | over 60 " | 4 |

ered, 23 days. Thirteen were treated within 48 hours after the onset with one death. This patient showed initial improvement but developed empyema, peritonitis and intestinal obstruction. The seriousness of the disease in the older age groups is shown in our series.

Positive blood cultures were present in five of the seven fatal cases but in none of those which recovered, though in several more than one culture was taken. Of equal if not more importance in determining the fatal outcome were the complications that were not directly related to the pneumonia. Two had very severe spasmodic asthma, one intestinal obstruction due to general peritonitis, one, a diabetic with paralytic ileus, had a large intestinal hemorrhage, and one died of coronary occlusion. A prompt but temporary detoxication followed the institution of treatments in two of the cases, but in each complications proved fatal.

Recovered Cases. Eighteen patients recovered (table 3) but what part the treatment played in any individual case is difficult to say, for who has not seen the utterly hopeless case recover without any special treatment and the mildest case become suddenly fulminating? Yet those of us who saw the cases most intimately were of the opinion that when a successful compression could be obtained early, the patients were not only much more comfortable but seemed to be quite promptly detoxicated. In a number, the course of the disease seemed to be shortened. Yet in seven of the cases which recovered, it did not seem that one could attribute the recovery to the treatment as their course did not seem to be influenced by it. In some the treatments were too far apart. Two had been ill a long time when treated (six or seven days). One did not appear seriously ill and was given a single injection for the relief of pain but we felt he would have recovered without it.

As has been said, the most satisfactory results were obtained when the treatment was administered early and when adhesions were absent or did not interfere with compression. (Charts 1 and 2.)

The question of "aborting" pneumonia before there is radiographic evidence of the lesion is an intriguing one. Unfortunately at this time the physical signs are also indefinite. Some who saw one of our cases felt that pneumonia was probably aborted, though others were skeptical. (Chart 4.) We have seen the roentgen-ray films of a similar case in another hospital where treatment was not given on admission because of a lack of radiographic evidence. Films taken a few hours later, however, demonstrated the lesion. The roentgen-ray may show an apparent increase in the amount, or degree, of consolidation when the patient clinically shows great improvement. This sometimes occurs following the use of specific serum.

Six of our cases had bilateral involvement (24 per cent) and two of these died (35 per cent). Five of the six received bilateral injections with one death (20 per cent). Two of these, however, also received type serum.

TABLE III
Recovered Cases

| H H Num- ber | Age Sex | Type Site | Dry Dis | Bld Cult | No Treat Total Amt | Relief Pain | Prompt Detoxi- fication | Dry Dis Temp 100 | Day Serum Given | Complications Comments |
|--------------------|------------|----------------------|-------------------|-------------|---|----------------|-------------------------------|---------------------------|----------------------------|---|
| 287435 M F | 22 F | IV L l | 6 | — | 3 700 cc | ? | ? | 10 | No | Adhesions +2 Time onset? Following influenza Annoying cough not re- lieved by treatment |
| 286098 J H | 41 M | IV R l | 2 | — | 1 250 cc | +3 | never toxic | never higher | No | Very mild case Definite onset, chill, bloody sputum but not toxic |
| 287055 L S | 44 M | III R u | 3 | — | 2 650 cc | +2 | +3 | 4 Chart I | No | Adhesions +1 |
| 285304 J B | 24 M | IV R u | 3 | — | 4 970 cc | | +3 | 7 | No | |
| 287171 F M | 16 M | IV R l | 2 (42 hrs) | — | 5 1700 cc | +3 | +3 Chart | 4 | No | |
| 287659 L C | 54 F | Not determ R l | 2 | — | 5 2300 cc | +3 | +3 | 4 | No | |
| 287989 R R | 17 F | I L l R m | 2 | — | 4 2L 900 cc 2R 500 cc | +3 | +3 | 4 | 3 90 000 units | Adhesions +2 Bilat involvement Serum given after spread |
| 291860 A S | 40 M | II L l | 1 (23 hrs) | — | 7 6L 2650 cc 1R 200 cc | +2 | — | 4 | 3 100 000 units | Adhesions +2 Serum given after spread |
| 288501 J B | 68 M | I L l | 5 chart 8 | — | 5 1600 cc | +1 | +3 | 9 | No | Adhesions +2 |
| 288555 G D | 46 M | II L l | 2 | — | 5 1900 cc | +1 | +3 | 6 | No | Adhesions +2 |
| 288108 W B | 14 M | II L l | 1 (13 hrs) | — | 11 6L 2100 cc 5R 1800 cc Decompressed 1600 on L | ?? | +1 | 5 | No | Adhesions +2 Spont pneumothorax? Congenit heart disease Bilat involvement |
| 288608 H G | 38 M | II L l | 1 (15 hrs) | — | 4 1550 cc | No | No | 13 | 2 and 3 90 000 units | Adhesions +2 Air treatment no result Small Plv effus |
| 288312 J L | 13 M | IV R l m | 7 *sec text | — | 6 1130 cc | No | No | 13 | No | Adhesions +3 Pt treated seventh day af- ter onset of lesion lower right lobe and 24 hrs af- ter spread to right upper |
| 287443 A C | 33 M | IV R u | 2 | — | 3 1300 cc | No | +2 | 3 Chart II | No | |
| 289122 D H | 55 F | III L l R l | 2 (30 hrs) | — | 7 4L 375 cc 3R 450 cc | No | +1 | 6 | No | Adhesions +3 Pt wildly delirious |
| 289363 A M | 28 M | IV L l | 2 (29 hrs) | — | 7 2025 cc | +3 | +3 | 3 | No | |
| 289431 R C | 38 M | IV R l m | 3 | — | 6 1700 cc | No | No | 8 | No | Adhesions +3 Course unmodified |
| 290000 A K | 16 M | I R l | 2 (26 hrs) | — | 8 2300 cc | +2 | +2 | 7 | No | Adhesions +2 Detox followed treatments but never complete |

* Due to low I Q of patient difficult to determine

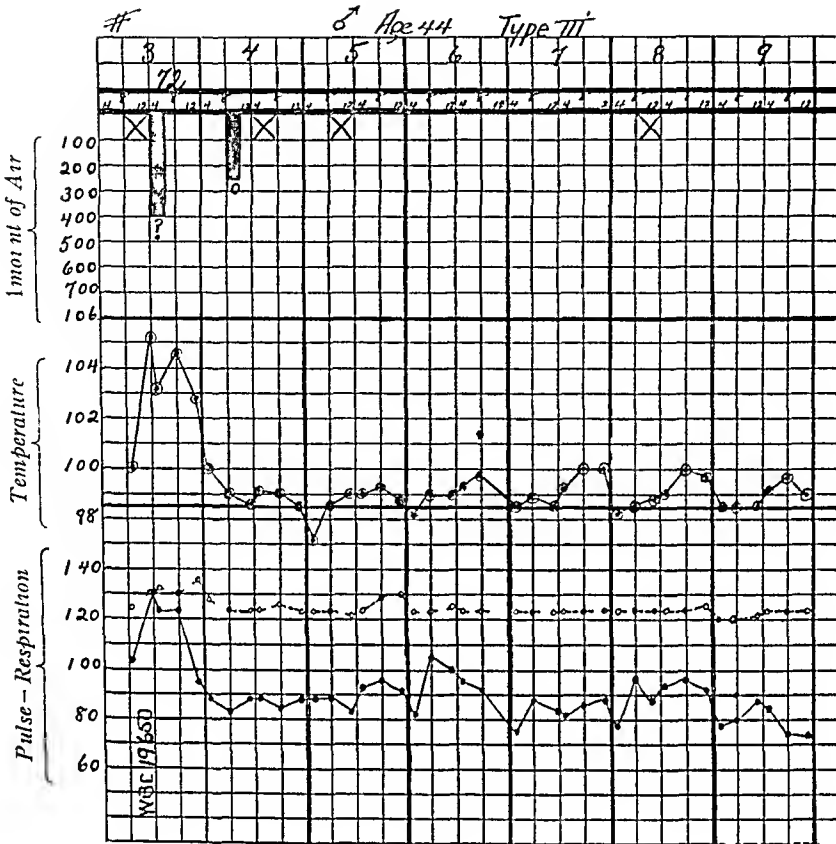


CHART I

LS, male, age 44, type 3, Ru, third day of disease, WBC 19,650 82/18, blood culture negative. He was given 400 cc shortly after admission. A profuse sweat followed with complete detoxication. The next morning, though he appeared well, he was given another injection of 250 cc. At the conclusion of both treatments the mean intrapleural pressure was slightly negative.

Especial attention is drawn to the fact that he received an injection after the temperature was normal and he seemed well. We did not at this time appreciate the importance of this extra treatment.

when the spread to the contralateral lung took place. These will be reported separately.

DISCUSSION

Frequency of Treatment As the result of many years of experience in treating tuberculosis with pneumothorax, our early cases were given moderate amounts with a negative mean pressure at the conclusion. The interval between treatments in the early cases was about 12 hours. Several of the patients so treated appeared to be benefited. In some the pressure was zero (atmospheric) but in all of these, as has been said, the pressure would become positive with each cough. In a few the final mean pressure was plus two or three cm. of water. As the lymph stasis and the

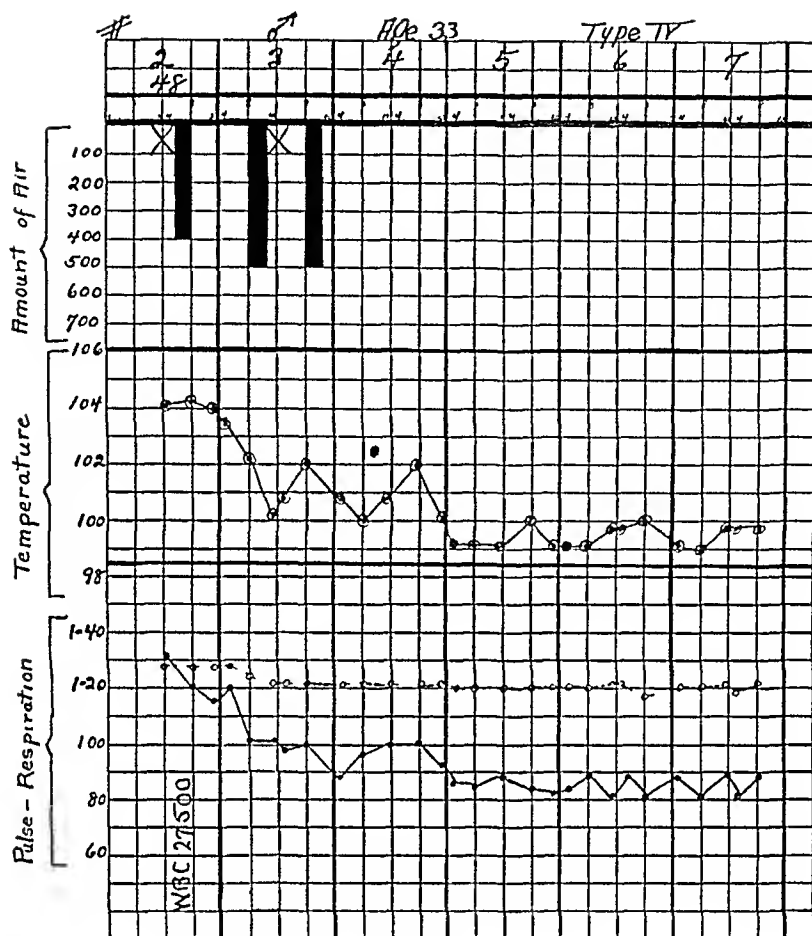


CHART II

A C, male, age 33, type 4, second day (48 hrs), WBC 27,500 82/18, blood culture negative. He appeared to be a moderately severe case. He was given 1400 cc in three injections. Following the first there was a marked drop in temperature and pulse. The next two treatments were given at just the right time before the temperature rose, i.e. before the lung expanded. He appeared to have no adhesions.

diminished blood flow in the collapsed lung result in a decrease in circulating toxins, the first three or four treatments should be given at intervals of four to six hours. *It is particularly important when clinical improvement follows and the temperature falls to normal, to give another injection promptly* because with the slight expansion of the lung, the temperature is apt to rise and the toxemia to reappear. This is well shown by charts 1 and 4.

The Optimum Pressure Of all who have employed this treatment in pneumonia, Blake alone advocates complete collapse of the whole lung as promptly as possible, maintaining this during the first 24 to 48 hours by frequent refills. He employs large amounts of air and aims to keep the mean intrapleural pressure positive at all times. Analysis of his cases



CHART III

RC, male, age 38, type 4, third day, R1 and m, WBC 20,600, blood culture negative. Vague history of ill-health. The house officer thought he had a pleural effusion, so no injection was given on admission. The next morning he had bronchial breathing over the right lower lobe but there was also an area of bronchial breathing near the lower angle of the left scapula. Fearing a possible bilateral process, we postponed the treatment several hours until another roentgen-ray film showed the left lung to be clear at which time 400 cc were injected. Five and one-half hours later 550 cc, seven hours 100 cc, 11 hours no injection as the mean intrapleural pressure was plus 1 cc, 16 hours 400 cc, 16 hours 50 cc. The pressure was slightly positive at end of each treatment but the patient never perspired and his pain was not relieved. The roentgen-ray showed the lung to be adherent to the diaphragm.

When we find we can introduce only a small amount of air after several hours (in this case 50 cc after 16 hours) in a patient who has readily taken larger amounts, we have found that serum has formed. In this case 70 cc sterile serum were aspirated. The temperature fell gradually as one would expect in the untreated case. Three times readings of intrapleural pressure were taken but no air injected as pressure was positive (♂).

appears to show that the cases so treated received the greatest benefit. All the others who have used this treatment endeavored to compress the lung rather than to collapse it and have kept the intrapleural pressure slightly negative or neutral.

We seriously question the wisdom of employing large amounts (800 to 1000 cc) in patients exhibiting evidence of marked arteriosclerosis as it seems possible that a change in blood flow through the sclerotic vessels might occur as the result of the mediastinal shift and serious results follow. On the other hand, it may require slightly positive pressure at the first few treatments to secure adequate compression and to separate the freshly adherent pleural surfaces.

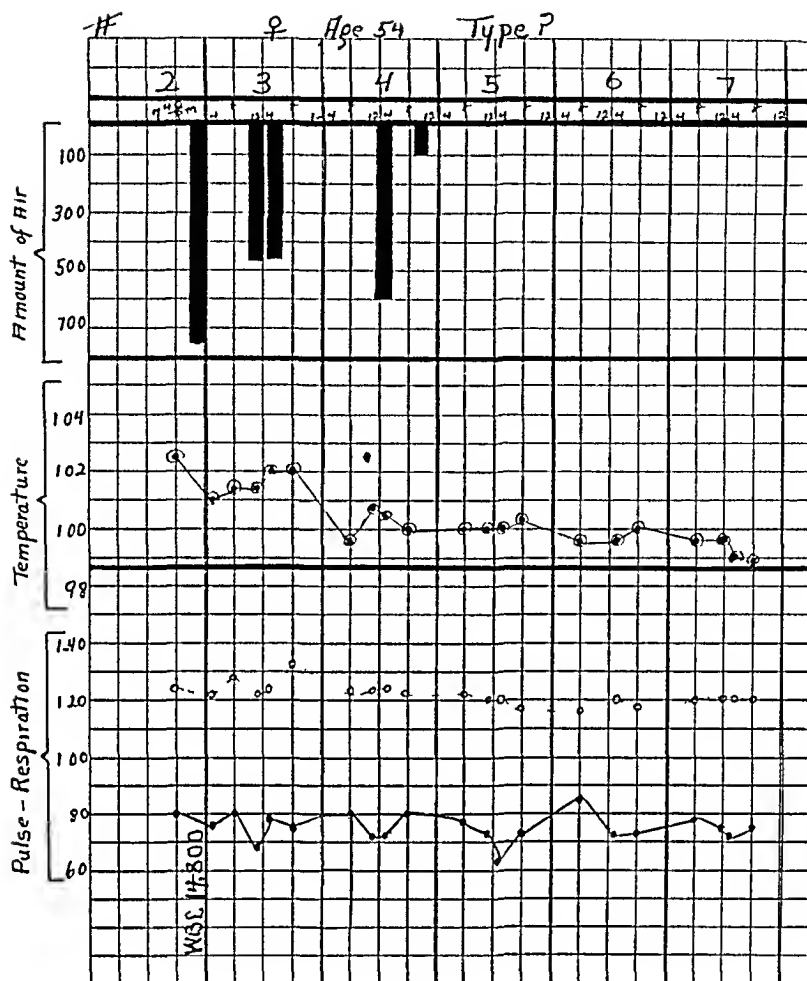


CHART IV

EC, female, age 58, type not determined, R1 ?, onset 24 hours or less, WBC 14,800 83/17, blood culture negative. A month prior to present illness patient had a cold of several weeks' duration with pain in right lower chest and a chill that was repeated shortly before admission also the day before admission she began to cough, with greenish expectoration. She appeared moderately toxic. There was diminished expansion due to pain in right side, and a questionable dullness and a few fine rales were heard over the lower lobe.

She was given five injections, the first of 750 cc, and 2300 cc in all were given. The pressure was slightly positive after the last two treatments, the others slightly negative. Pain was greatly relieved and the toxic symptoms promptly subsided.

Roentgen-rays on admission: "No definite evidence of pneumonic consolidation. The peribronchial structure extending into the basal portion of the right lobe posteriorly towards the mediastinum is exaggerated. The heart appears retracted slightly to this side and the right diaphragm is slightly elevated. These findings are compatible with the congestion of a beginning pneumonic type of process or partial atelectasis of the lower lobe."

When large amounts of air have been injected with resultant shift of the mediastinum, we have frequently noted some increase in the peribronchial markings in the roentgen-ray film and a few times a general haziness of a considerable part of the contralateral lung, which promptly

subsided following decompression. We suspect this to be due to some interference with the lymph and vascular circulation rather than to atelectasis. In one case (W B) whose several injections were given on both sides because of a spread a spontaneous pneumothorax apparently developed. Several hundred cubic centimeters of air were aspirated. The patient recovered.

A change in the position of the trachea is the best indication of mediastinal shift. Several years ago, Webb, Forester and Gilbert¹¹ described a simple and very accurate clinical method of determining its position. Their technic has proved of great value in our cases and on the whole it is as accurate as the roentgen-ray.

Pleural Effusions How frequently lobar pneumonia is accompanied by the collection of serum in the pleural cavity is unknown. None of Lieberman and Leopold's dogs that died had any pleural effusion. The roentgen-ray evidence of small amounts (100 c c or less) is not conclusive though we have learned to regard a slight ground-glass appearance as suspicious. Following air injections when films are taken in the upright and lateral positions, very small amounts can be identified.

Serum was present in 15 of our cases, usually in small amounts. The maximum amount was 700 c c. Whether the frequency of its occurrence and the amount depend upon the pressure used is not known. It would seem as if its incidence might be increased by positive pressure. The temperature of the air introduced may also be a factor. When after an interval of several hours following an injection of several hundred c c of air, the intrapleural pressure has not fallen or has become positive, serum has probably begun to form. Pneumococcus empyema developed in three cases with two deaths. One of these two had peritonitis and intestinal obstruction, and the other patient, aged 75, had severe asthma. In the third case, several unsuccessful attempts were made to locate a small encapsulated empyema and once, when zeal exceeded judgment, the needle was introduced too low, as the subsequent roentgen-ray showed a small amount of air below the diaphragm. There were no untoward symptoms and the air was promptly absorbed.

Adhesions Evidence has been presented in the case reports that the most serious obstacle to this form of treatment is adhesions. Even patients who recall no previous pulmonary disease are often found to have them. They were present in 19 of our 25 cases and in 13 of those who recovered. Our earliest case, treated 15 hours after the chill, had such extensive adhesions that the pneumonic site could not be compressed. When the relief of pain during a treatment is followed by a pulling sensation, referred usually to a different area, the presence of an adhesion is suggested. Adhesions are especially difficult to combat when present over the lower lobes. The lung that is stuck fast to the diaphragm is the most serious obstacle to this treatment.

The earlier the treatments are started the easier it is to separate the pleural surfaces. When a string type of adhesion is met with, one should always realize the possibility of a spontaneous pneumothorax if positive pressure is used. If adhesions are extensive and do not appear to be giving way after three treatments and the patient has not shown definite clinical improvement, further injections will probably prove unavailing.

SUMMARY

1 The pneumothorax treatment of pneumonia is safe when properly carried out but experience in pneumothorax technique is a prerequisite.

2 Pleural adhesions are very common, especially in the elderly, but unless extensive, a satisfactory result can often be obtained unless their location prevents compression of the site of the lesion. In our series they prevented an entirely satisfactory compression in nearly 30 per cent of the cases. When the lower lobe is involved and adherent to the diaphragm, the results are unsatisfactory.

3 If adhesions are not present, pain is at once relieved, respiration is deeper and sleep follows, sometimes during the treatment. Morphine is not needed and only an occasional dose of codeine is required.

4 Cases adequately treated within the first three days will usually show complete detoxication with fall of temperature and profuse sweating within 12 hours, though the temperature may not remain down until a day or two later. Treatment is of little value after the third day.

5 The first three treatments should be given at intervals of four to six hours and it is advisable to give one more treatment when the temperature reaches normal even though the patient may appear to have completely recovered.

CONCLUSIONS

When compression can be effected early and maintained, pain is relieved and a prompt lessening of the toxemia is to be expected. It is probably the best treatment for the types for which there is no anti-serum. Due to the frequency with which adhesions occur, it cannot supplant the use of serum in suitable cases (Types I and II). However, not infrequently one may secure the benefits of a satisfactory compression before the type has been determined.

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THE OCCURRENCE OF CORONARY AIR EMBOLISM IN ARTIFICIAL PNEUMOTHORAX¹

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ALTHOUGH an embolism is an infrequent complication of diagnostic and therapeutic measures, it is so startling and dramatic in its manifestations as to have been long a subject of great interest. Its occurrence has not been limited to any one field of medicine. Otolaryngologists have reported cases following antrum puncture (Garding,¹ Bacher²). Gynecologists have observed the condition in induced abortion, and also in version in cases of placenta praevia (Fink,³ Gough⁴). In the field of general surgery it has apparently been most common in operations on the neck. This is probably due to the size of the venous channels in this region. Chest surgeons and those employing pneumothorax therapy, however, have encountered this complication more frequently than any other group. The reason for its more frequent occurrence in operative procedures involving the lungs as compared with those dealing with other organs is readily understood. Large quantities of air can be injected slowly into the systemic veins without harm (Schlaepfer,⁵ Jackson and Babcock,⁶ Bergstrand,⁷ Joannides and Tsoulos⁸). On the other hand, as little as 0.5 to 1.0 c.c. of air in the left heart or carotid artery (comparable for practical purposes to air introduced originally into the pulmonary veins) may be fatal, as shown experimentally by Schlaepfer,⁵ Stepp and Parade,⁹ and others.

The clinical picture observed in cases of air embolism due to the introduction of air into the pulmonary veins is variable. In most cases the patient complains first of giddiness or faintness, and then lapses suddenly into unconsciousness with convulsions, which may be generalized or Jacksonian in type. The pupils are dilated and there is often conjugate deviation of the eyes. Circulatory collapse is a prominent feature. Death may follow or there may be gradual recovery. In non-fatal cases monoplegia or hemiplegia may persist for a variable period of time. Transient blindness or aphasia is relatively common. Air bubbles have been observed passing through the retinal vessels (Wever¹⁰). Neurological findings are not always present, however, some cases being characterized by unconsciousness and circulatory collapse only.

In the past the clinical picture just described has been widely attributed to "pleural shock" or "pleural eclampsia", a condition supposedly of reflex origin. That irritation of the inflamed visceral pleura by various means does in some cases produce vago-inhibitory phenomena, and in others vasomotor disturbances, has been conclusively demonstrated by Capps and

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Lewis¹¹ Their experiments failed, however, to reproduce a picture identical with that observed clinically. In their experiments no neurological signs suggesting focal lesions in the central nervous system occurred. On the other hand, Wever,¹⁰ Schlaepfer,¹² Rukstinat,¹³ and others have shown that the injection of air into the carotid artery or left ventricle in animals produced signs and symptoms similar in every respect to those seen in patients. At the present time phthisiologists and chest surgeons are generally in accord with the view that pleural reflexes may account for some of the less serious accidents complicating artificial pneumothorax and other thoracic operations, but that those cases presenting features of the severity described above are due to air embolism.

Artificial pneumothorax is the procedure most frequently complicated by air embolism. In most cases it is the attempt to induce pneumothorax, or the attempt to reclaim a lost pneumothorax pocket that results in the wounding of a pulmonary vein with consequent air embolism. However, in cases with an established pneumothorax the needle may enter a vessel in an adhesion with the same result. It is to be emphasized that many cases have occurred in which no air has been injected. There is sufficient air in the tubing of the pneumothorax apparatus to cause serious embolism if it is sucked into a pulmonary vessel. This fact led Cobbs¹⁴ to suggest that, in inducing a pneumothorax, the needle be introduced with the bottles of the pneumothorax apparatus so adjusted that there would be a negative pressure of 4 to 5 cm. of water in the tubing. This maneuver does not prevent air entering a wounded vein by means of a broncho-venous fistula, should such an injury be produced by the needle, but is distinctly of value in giving a certain degree of protection.

Estimates as to the frequency of air embolism as a complication of artificial pneumothorax vary considerably. Probably a fair estimate would be about once in every 2000 to 3000 refills. One might expect the condition to occur more frequently, but it is probably true that an injured vein will not, in most instances, permit the entrance of air unless it is held open by indurated lung tissue (Schlaepfer).

Throughout the literature dealing with the clinical picture in air embolism, emphasis has been placed on the obstruction of the cerebral vessels as the important factor in the causation of death. Recent studies, however, indicate that air in the coronary arteries plays a very important rôle in the fatal outcome. Rukstinat and LeCount's¹⁵ experiments are of particular interest. Working with guinea pigs, these investigators produced broncho-venous fistulae by raising the intra-tracheal pressure sufficiently high to rupture alveoli into adjacent blood vessels. Convulsions were invariably produced when the pressure was raised to 30 mm. of mercury. A pressure of 45 mm. of mercury always resulted in death in 50 to 75 seconds. Necropsy, carried out under water, revealed air in the coronary arteries in all the animals. There was a 50 to 90 per cent filling of the coronary channels with air. Hemorrhages in the myocardium were noted in some instances.

More recently Rukstinat¹³ has published the results of further studies on coronary air embolism, using the dog as the experimental animal. In these experiments the rapid injection of air into the coronary arteries was immediately followed by tumultuous heart action, and acceleration which gave place within 10 to 20 seconds to pronounced slowing of the heart rate. Death occurred in one to four minutes. Air injected slowly in amounts up to 20 c.c. caused only temporary cardiac disturbances. No statement is made as to whether or not infarcts developed in any of the animals which recovered, and no electrocardiographic studies were carried out. Air injected into the left auricle caused death from coronary air embolism in 35 to 70 seconds. Left auricular injections were likewise fatal in a group of animals in which the carotid and vertebral arteries had been ligated 15 minutes previously, in order to eliminate cerebral embolism as a factor in the fatal outcome. Rukstinat concludes from his experiments that obstruction of the coronary arteries must be considered of great importance in all cases of air embolism originating in the pulmonary circulation.

A search of the literature reveals only one experimental study dealing with electrocardiographic changes in air embolism. Stiatman and Uhlenbrück,¹⁴ using the dog as the experimental animal, took electrocardiographic tracings following the injection of air into the femoral vein. Various disturbances of rhythm, and changes in the form of the P, QRS, and T-deflections, were noted. The striking feature of the tracings presented by these authors, however, is the presence in some of monophasic deflections of the type seen clinically and experimentally in the early stages of coronary occlusion. No statement is made, however, as to the presence or absence of air in the coronary arteries at necropsy. In one of the animals air had passed through the pulmonary capillaries in sufficient quantities to be found in the systemic arteries.

Clinical reports of coronary air embolism are few in number, possibly because the interest of the observer has been centered on the cerebral manifestations. Jackson and Babcock⁶ report a case in which sudden death occurred during an open operation for empyema in a male, aged 23 years. There was systolic arrest of the heart. This, the authors believed, was due to coronary air embolism, although no statement is made as to the actual observation of air in the coronary arteries.

Pollak¹⁵ reports a case in which the coronary vessels were filled with air at the time of the postmortem examination. The patient had developed a spontaneous pneumothorax, which was treated by the aspiration of air. One hour following the aspiration, the patient suddenly collapsed and became markedly cyanotic. Death ensued a few hours later.

The following case is of particular interest because electrocardiograms were taken both before and after the apparent occurrence of coronary air embolism during an attempt to produce artificial pneumothorax for the treatment of pulmonary tuberculosis.

CASE REPORT

An unmarried woman, aged 24 years, was admitted to the Tuberculosis Unit of the University Hospital on July 28, 1932, with a history of four attacks of pleurisy during a period of five years. There had also been cough, productive of a moderate amount of purulent sputum, ease of fatigue, and loss of 12 pounds in weight. The patient had been told in 1931 that she had "leakage of the heart." Physical examination showed rales at the left apex and signs of cavitation in this region. The heart showed no evidence of enlargement, but there was a rumbling systolic murmur heard over the entire precordium, with its maximum intensity in the pulmonic area. The systolic blood pressure was 115 mm Hg, the diastolic 75 mm. The remainder of the physical examination was negative except for a right dorsal, left lumbar, roto-scoliosis. The sputum examination was positive for tubercle bacilli, in large numbers. The roentgen-ray examination of the chest (figure 1) showed a cavity at the left apex 4 cm in diameter, with several small annular shadows below it, which were interpreted as additional cavities. There was a considerable increase in density in the second left anterior intercostal space. The right lung field was clear except for a small, irregular, adventitious shadow in the second anterior intercostal space. The electrocardiogram on August 1, (figure 2a) showed marked right axis deviation, but was

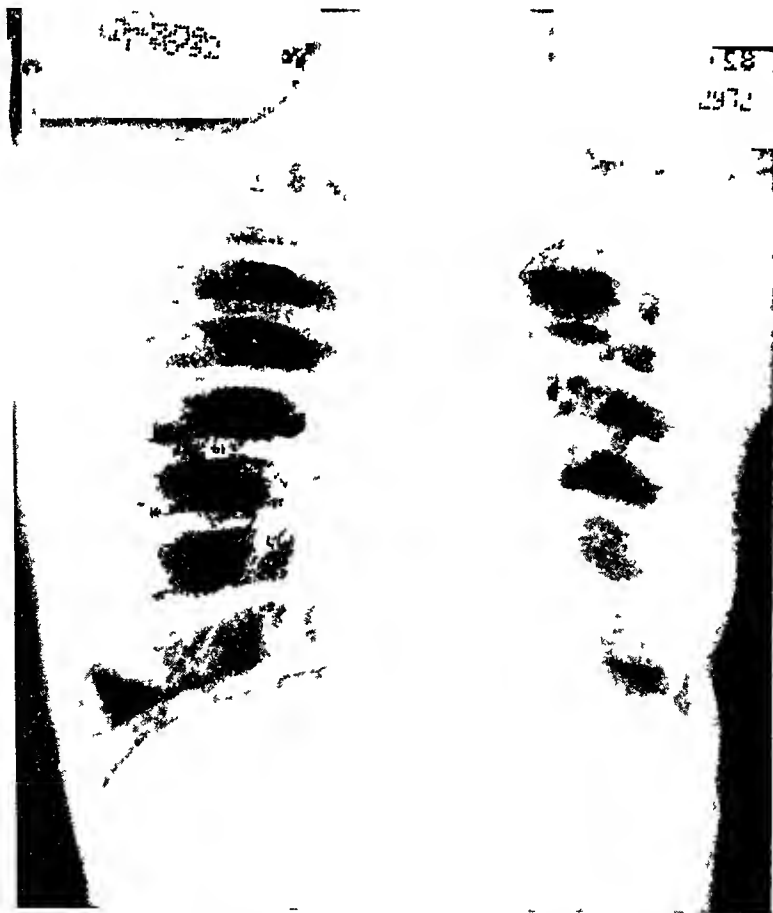


FIG 1 Roentgen-ray of the chest taken July 28 1932, showing predominantly unilateral tuberculous process with cavitation

otherwise negative. The presence of marked right axis deviation in a patient with a systolic murmur of the type described was felt to justify the diagnosis of pulmonary stenosis.

Artificial pneumothorax on the left being the therapeutic procedure of choice in this case, attempts to induce it were made on three different occasions, but without success. On the fourth attempt on August 8, the needle was introduced in the lower left axillary region, with the patient on her right side. The needle had just been introduced, and no manometer oscillations had been obtained, when the patient complained of feeling faint. The needle was immediately withdrawn, but a generalized convulsion lasting about 30 seconds ensued. Following this the patient was markedly cyanotic, there was slowing of the respirations and the pulse could not be felt. Adrenalin and caffeine were administered subcutaneously. Soon after this there was recovery from the circulatory collapse and respiratory depression. When the patient became fully conscious she complained of substernal pressure. She was obviously dyspneic, and vomited frequently. An emergency chest roentgen-ray showed no pneumothorax pocket. The sensation of substernal pressure and the vomiting persisted for several hours and the patient complained of dyspnea for a period of six days following the accident. Thereafter there were no further symptoms referable to the incident and the only indication of persistent change resulting therefrom was an electrocardiographic abnormality.

An electrocardiogram was taken 2 hours and 55 minutes after the accident. This is reproduced in figure 2b. Subsequently, electrocardiographic tracings were taken at frequent intervals, and representative curves are reproduced in figure 2.

It is of interest to add that the patient's tuberculous lesion eventually became quiescent, thanks to a phrenic nerve interruption on the left, which was successful in completely closing the large cavity.

COMMENT

The feature of greatest interest in this case is the series of electrocardiographic changes which followed the accident described. These changes are typical of myocardial infarction. This is true not only of the progressive alterations in the form of the RS-T segment and T-deflections (figure 2b, c, and d), but also of the changes in the form of QRS. The initial upstroke of the QRS group in Lead I, present prior to the accident (figure 2a), is absent in the subsequent curves (figure 2b, c, d), in which it is replaced by a prominent Q-deflection. Changes of this kind in the QRS-deflections have been shown by Wilson and his coworkers¹⁸ to be associated with infarction of the anterior wall of the heart. When they are associated with sharp inversion of the T-deflection in Lead I, as in the present instance, there can be very little question as to the presence of a localized lesion in the anterior ventricular wall.

As a possible cause for the myocardial disturbance suggested by the patient's symptoms and shown by the electrocardiogram we may consider three possibilities: (1) Injury to the heart by the pneumothorax needle, (2) coronary thrombosis, (3) coronary embolism.

Injury to the heart by the pneumothorax needle is mentioned because either pericarditis or hemorrhage into the pericardial sac may produce changes in the T-wave and S-T segment of the electrocardiogram suggestive of coronary occlusion. However, in this case the needle was intro-

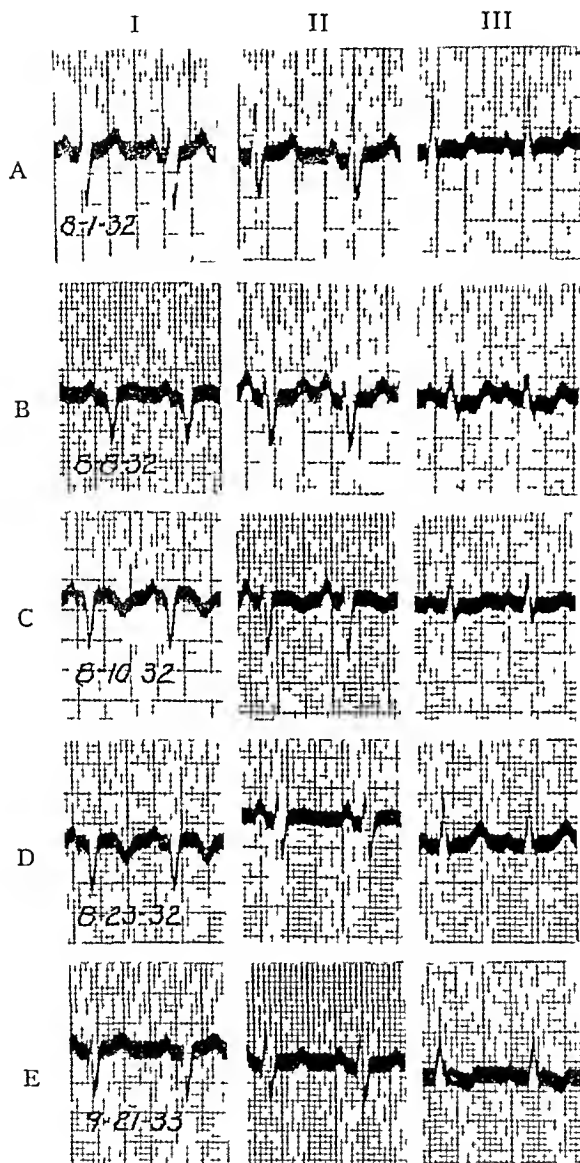


FIG 2 Series of electrocardiographic tracings selected to demonstrate progressive changes in initial and final ventricular deflections

(a) Curve taken prior to the embolic accident showing right axis deviation

(b) Curve taken 2 hours and 55 minutes after the embolic accident The initial upstroke of the QRS deflection in Lead I, noted in *a*, is now absent, and there is a large Q-wave in this lead The S-T segment is elevated in Lead I and depressed in Lead III

(c) Curve taken two days later There is now present in Lead I, in addition to the prominent Q-deflection, a definite coronary type of T-wave inversion The T-wave in Lead II is also inverted

(d) Curve taken 15 days after embolic accident The coronary type of T-wave in Lead I is again present in this tracing T is now upright

(e) Curve taken 13 months after the accident There is now a reappearance of the initial upstroke in Lead I and the T-waves are normal

duced in the mid-axillary region, and to such a slight depth that this possibility is precluded. Furthermore, neither pericarditis nor hemorrhage into the pericardial sac produces changes in the initial ventricular deflections of the type seen in the present instance.

Coronary thrombosis as a cause of the myocardial infarction is practically excluded by the patient's age. There were, furthermore, no evidences whatsoever of any vascular disease, and the recovery of the patient from the cardiac standpoint has been practically complete. There is no obvious reason why coronary occlusion should complicate an attempt to produce pneumothorax and its occurrence as a pure coincidence is too remote for consideration.

Coronary embolism must, therefore, be considered as the only likely cause of myocardial infarction in this case. Whether the embolus was air or a clot cannot be stated with certainty. Vallin¹⁹ has suggested that the mobilization of thrombi in the pulmonary vessels in the course of thoracentesis might result in embolism. Such an embolism must be considered a possibility in this instance. Saphir,²⁰ however, has pointed out in his review of the literature on the subject the extreme rarity of cases in which a solid type of embolus finds its way into the coronary arteries. It is far more logical, in view of the work of Rukstinat, to consider air the embolus responsible for the cardiac disturbance described.

One question naturally arises from the assumption that coronary air embolism was responsible for the electrocardiographic changes. This concerns the possibility of air remaining in the coronary arteries long enough to produce death of the heart muscle, or at least to produce changes lasting several weeks. This is a difficult question to answer. The experimental work which has been done has yielded no evidence for or against the possibility. Only by considering a somewhat analogous situation, the results of cerebral ischemia in cerebral air embolism, can a partial answer be given.

In cerebral air embolism the monoplegias and hemiplegias which result from ischemia of brain tissue are of variable duration, but it is important to emphasize that there are cases in which the paralyzes persist for many days or even months. In one case observed by Villani²¹ a complete left hemi-paresis persisted for four months, and a paresis and atrophy of the left arm were present until the patient's death from tuberculosis 28 months after the original embolic accident. Such persistence of paralysis can only be accounted for on the basis of profound changes in the cerebral tissues. Wever,¹⁰ in his experimental study of cerebral air embolism, points out that, within 15 hours of air injection in dogs, liquefaction of brain cells is noted and that in three to five days there is a marked proliferation of the glial cells at the places where brain cell injury is marked. Cerebral tissue is, of course, more susceptible to injury by vascular changes than cardiac muscle, but it seems logical to assume that the changes produced by coronary air embolism are as lasting as those produced by cerebral air embolism.

SUMMARY

A case of coronary air embolism complicating the attempted induction of artificial pneumothorax is reported. This case supports the contention of Rukstinat that involvement of the coronary arteries is an important factor in air embolism complicating artificial pneumothorax and other chest procedures.

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THE SHOCK SYNDROME IN MEDICINE AND SURGERY ¹

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WITHIN the past five years renewed attention has been directed to the shock syndrome. Several investigators have obtained results at variance with interpretations previously held. Yet those interpretations were advanced by men of international standing and were based upon experimental work and observations which have been adequately verified by repetition at the hands of others. The dissenting views likewise are based upon experimental evidence of apparently equally high credibility. An attempt to correlate the contradictory phases of the evidence seems appropriate. All the facts which studies on shock have established may be assembled into an intelligible picture. This problem becomes relatively simple when its parts are appropriately correlated. One fundamental concept must be comprehended. *The shock syndrome results from a disparity between the volume of blood and the volume-capacity of the vascular system.* All the pertinent facts regarding shock may be assembled about this concept as a skeletal frame. Its conditions of occurrence must be sought among factors which (a) decrease the volume of blood, (b) increase the volume-capacity of the vascular system, and in combinations of factors *a* and *b*.

Such a disparity produces circulatory failure with certain well known characteristics. Rapid weak pulse, low blood pressure, rapid shallow respirations, decreased temperature and pale clammy skin are prominent features. Vomiting and diarrhea are frequent, and these discharges often are blood-tinged. This condition is accompanied by a diminution in blood volume and by marked hemo-concentration. The hemoglobin and red cells are usually increased by 20 to 50 per cent. This feature provides a valuable clinical test for recognizing shock and for differentiating it from hemorrhage or other conditions. Attention is invited to a brief consideration of the mechanism by which shock develops, and of the factors concerned.

Decreased Volume of Blood. Loss of blood by hemorrhage produces a disparity by decreasing directly the volume of blood. This results in the characteristic features of shock with these exceptions: following hemorrhage the concentration of blood is lowered, and the decreased volume may be restored by the injection of fluids. In shock from other causes the concentration of the blood is increased, and injections of fluid are usually ineffective.

A decreased volume of blood may develop indirectly by the transudation of plasma through the walls of capillaries whose permeability has been increased by various agents to be discussed later. Increased capillary permea-

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bility is present in shock from various causes, and produces the hemo-concentration which is so characteristic of this condition

Increased Volume-Capacity of the Vascular System Normal tissues have a supply of capillaries adequate to their maximal circulatory needs. Normally only a small fraction of these are open to circulation simultaneously. If all the capillaries in the skeletal muscles alone were open simultaneously, their volume-capacity would be sufficient to contain the entire blood of the body (Krogh). Other areas, as the respiratory system or the gastrointestinal mucosa, have an equally large supply of minute vessels. Under conditions to be discussed, these minute vessels become atonic, relaxed and unresponsive to nerve impulses or other agents which normally produce contraction (Krogh, Hooker). They withdraw blood from circulation like a sponge absorbs water. The volume-capacity of the vascular system is greatly increased. The circulation fails not because of cardiac weakness, but because of insufficient return of blood from the tissues. The heart is not a suction pump, it cannot draw blood out of the tissues, it can only pump the fluid supplied to it.

Many conditions may produce capillary atony and dilatation. The experiments of Dale and his associates showed that intravenous injections of histamine produce this type of circulatory failure. The capillaries and venules were dilated and filled with blood, their permeability was increased, edema of the tissues and hemo-concentration occurred, the blood volume was decreased by 40 per cent, blood pressure fell to low levels, and the animals died with the characteristic evidences of shock.

Traumatic Shock A wealth of observations on traumatic shock was published during and immediately following the World War*. It was shown that shock is accompanied by an increased concentration of blood and by a marked diminution in the total volume of blood in circulation, that the fall in blood pressure is not due to cardiac weakness or to vasomotor deficiency. The hearts of patients and of experimental animals in shock were able to maintain normal blood pressure if supplied with fluid and with vascular resistance, the arteries were not atonic but were contracted to the maximum.

The reports of these investigations indicate that traumatic shock results from the absorption of injurious substances from traumatized tissue, that these substances produce capillary dilatation and increased permeability resulting in stagnation of blood in systemic areas, that this sequestration of blood and the transudation of plasma into the tissue reduce the effective blood volume. Increased concentration of blood and the circulatory failure characteristic of shock result. Subsequent investigations have shown no discrepancies in this explanation but have corroborated its essential features.

It is remarkable that the gross and microscopic changes characteristic of shock escaped the attention of early observers. A number of workers noted

* Of especial value are the Special Reports 25 and 26 of the Medical Research Committee, London, 1919, H. M. Stat. Off.

such features as congestion, edema and capillary hemorrhages in the tissues in experimental shock. But no one emphasized that these visible changes are characteristic of shock, and are etiologically related to its development. Neither was it emphasized that observations on the concentration of the blood are useful in recognizing the shock syndrome clinically.

I have examined many records of postmortem examinations on soldiers following severe shell-fragment injuries. Marked congestion and edema of the viscera, and capillary hemorrhages in mucous and serous surfaces had been noted by the dissectors regularly in those who died of shock. Frequently such descriptive phrases as "wet autopsy" were used to denote the contrast with the "dry autopsy" seen following death by hemorrhage. But apparently no relation was seen between these findings and the shock mechanism.

Moon and Kennedy made gross and microscopic studies of the organs in experimental shock produced without local injury or hemorrhage. The characteristic manifestations of shock, including hemo-concentration, followed the implantation of small amounts of fresh, finely chopped dog muscle into the peritoneal cavities of normal dogs. Likewise, shock followed injections of sterile watery extracts of normal muscle, extracts of traumatized muscle, and was observed following trauma to the muscles of normal dogs. In each of these instances the postmortem findings were identical in character. Since these findings are of marked significance they will be described briefly for purposes of subsequent reference.

Experimental Shock Tissue Changes Characteristic of Shock The veins in subcutaneous and peripheral areas are collapsed and relatively bloodless. The viscera are deeply congested and have a purplish diffuse cyanotic color. This is especially prominent in the lungs, liver and gastrointestinal tract. The venules of the visceral peritoneum are engorged and distended. Those along the mesenteric attachment are especially prominent. Usually the spleen is contracted and bloodless, though occasionally it also is engorged. There are varying quantities of thin, blood-tinged fluid in the peritoneal, pleural and sometimes in the pericardial cavities. The mucosae of the respiratory and gastrointestinal tracts are swollen and have the appearance of red velvet. There are numerous petechial hemorrhages in the lungs, in the pleural and pericardial surfaces, in the intestinal mucosa, occasionally in the lining of the gall and urinary bladders, and in the meninges. Edema of the lungs and mucosae and serous effusions are most marked when shock develops gradually and death is not immediate. When shock ending in death develops rapidly, congestion and capillary hemorrhages are marked and edema is a less prominent feature. The fluid present in the stomach usually contains "coffee-grounds" flocculi which give a positive test for hemoglobin. The fluid in the stomach and bowel contains quantities of serum albumin. The undiluted fluid often forms a solid coagulum when heated.

On microscopic examination there are marked dilatation and engorge-

ment of the capillaries and venules in each of the organs mentioned. There are numerous minute areas of hemorrhage, apparently from dissolution of capillary walls, and tissue edema is present in varying degrees. The adrenals participate in these circulatory changes in a degree similar to that seen in other organs, but they show no other changes.

These observations indicate a widespread loss of tonus affecting the capillaries and venules. The circulatory disparity in this instance results from an increased volume-capacity of the vascular system or, what is equivalent, from inability of the vascular system to contract with its normal tonus upon the contained blood.

There was evidence that the minute vessels were abnormally permeable to blood plasma. This gave rise to edema, serous effusions, and to the transudation of fluid from the blood into the gastrointestinal canal. Such loss of fluid lowers the blood volume and produces hemo-concentration.

Experimental Shock from Poisonous Substances. Many chemicals and drugs produce injurious effects by causing atony and dilatation of the peripheral vessels, especially the capillaries and venules. Such substances are known as capillary poisons (Krogh, Heubner). Capillaries are exceedingly delicate structures and easily injured. Any condition or agent which injures them increases the permeability of their walls (Landis). This allows blood plasma to escape into the tissue spaces, producing edema and resulting in hemo-concentration. Heubner (1907) found that the intravenous injection of gold chloride was followed by a progressive decline of blood pressure ending in death in a few minutes. He gave the first detailed description and correct interpretation of the visible changes characteristic of shock, which I have found. The finest venules, especially in the abdominal viscera, were heavily congested. The peritoneal surfaces of the bowels were rose red or bluish red. The mucosae were dark red and contained numerous hemorrhagic flecks. Similar minute hemorrhages were present in the surfaces of the liver, spleen and kidneys. Blood-tinged fluid was present in the serous cavities. The lungs were deep red and contained numerous ecchymoses in their substance and also in the pleura. Blood flowed freely from the cut surfaces of the organs. The outstanding microscopic feature was distention and engorgement of the minute vessels in all the tissues. There were numerous capillary hemorrhages in the substance of the organs, especially the lungs, liver and kidneys. These are exactly the changes found in experimental shock. He concluded that the circulatory failure resulted from the widespread dilatation of the capillaries and venules. The animals had bled to death into their own capillaries.

Other poisons produce similar effects. MacNider found that the intravenous injection of mercuric chloride in dogs produced shock followed by death. Landis found that mercuric chloride 1:10,000 dilution, caused capillaries to become seven times more permeable than normal capillaries. Alcohol, urethane, veronal and other anesthetic drugs produce similar effects. Blalock, Robinson, Parsons and others noted that the barbitol anesthesia

which was used in experimental traumatic shock occasionally resulted in "spontaneous shock" when no experimentation had been done. I have seen a normal dog manifest the classical picture of shock following the intravenous injection of sodium pheno-barbital, 0.3 gm per kg of body weight. The blood pressure fell 94 mm in the course of three hours. Death followed a second smaller injection, and the postmortem findings were identical with those following shock from other causes.

Injections of peptone, albumose, or other products of protein cleavage will produce capillary dilatation and permeability resulting in the shock syndrome (Abel et al, Whipple et al, Krogh p 241). The same is true of injections of extracts of normal tissues (Delbet, Bayliss, Moon and Kennedy). Bacterial suspensions and toxins produce similar effects. Bacteria-free broth in which *B. Welchii* has grown, will produce shock if injected intravenously. I have produced the same effect by intravenous injection of killed broth cultures of enterococcus. This produced profound prostration, blood-tinged vomitus and diarrhea, rapid respiration and pulse, falling temperature, hemo-concentration and death within 48 hours. At postmortem the same changes were found as in shock from other causes.

The relationship between metabolic poisons and the shock syndrome rests largely upon clinico-pathologic evidence. The experimental use of metabolic poisons is impracticable, since they have not been isolated. It is known that bile is toxic, and that jaundiced patients frequently manifest toxemia. The rupture of a gall-bladder into the peritoneal cavity is followed by shock. The intravenous or intraperitoneal injection of sterile bile produces death with shock-like manifestations (Horrall and Carlson). At postmortem the characteristic evidences of shock are seen in the viscera. Apparently bile in sufficient concentration in the circulating blood is injurious to the capillaries, and produces effects like those of other capillary poisons.

Anoxemia Deficiency of oxygen is an important factor influencing capillary tonus (Cannon, Krogh, Heimberger, Landis). Anoxemia of relatively low grade, such as may be produced by temporarily occluding a vessel, causes dilatation and increased permeability of the capillary walls, with resulting edema and hemo-concentration.

Disturbances of Vasomotor Control It is well known that vascular tonus is influenced by nerve stimuli. Freeman found that prolonged arterial constriction, produced by the continuous injection of adrenalin or by hyperactivity of the sympathico-adrenal system, decreased the volume of blood in circulation. This was interpreted by him and by Cannon as due to partial asphyxia of the tissues resulting from maximal arterial constriction. However, the corpuscular elements were also decreased and there is no record that the subsequent condition was that of shock or that the pathological tissue changes characteristic of shock resulted. Erlanger and Gasser also found that injections of adrenalin caused a decreased volume of blood, but although they used larger doses than did Freeman, they were unable to produce other manifestations of shock by this mechanism. A

decreased volume of blood does not of itself constitute shock Is it possible that the arterial constriction merely caused a considerable volume of blood to be stored in the normal reservoirs, the spleen and liver?

Freeman attempted to produce shock by generalized vaso-dilatation Prolonged stimulation of the depressor nerve reduced the blood pressure from 145 to between 60 and 80 mm of mercury These low pressures were maintained for 95 minutes but returned promptly to normal upon cessation of stimulation The low pressures resulting from such vaso-dilatation were accompanied by a slight loss of blood volume but not by hemo-concentration These experiments did not produce shock

Eppinger found that low blood pressure, decreased blood volume and other evidences of shock followed the injection of cocaine about the vaso-motor center in the medulla The manifestations were not accompanied by a transudation of plasma through the capillary walls nor by hemo-concentration The circulation gradually returned to normal and the animals recovered without developing shock

Dale and Laidlaw found that acetyl choline produces marked arterial dilatation without affecting the veins and capillaries Thus its effect on the circulation resembles that of arterial relaxation from vasomotor insufficiency By slow infusion of acetyl choline the blood pressure was maintained at low levels for varying periods of time This did not result in capillary permeability or hemo-concentration The heart's action remained efficient and a return to normal occurred when the infusion was discontinued Shock did not develop in these experiments

It seems that one factor of the grave progressive shock syndrome is lacking in these experiments The tonus of the capillaries apparently is not affected, nor their permeability increased Hence edema and hemo-concentration do not develop It is conceivable that prolonged sympathico-adrenal stimulation or vasomotor inhibition might result in anoxemia or asphyxia of the capillaries This in turn would be followed by capillary dilatation and permeability, and would complete the picture Any lesion of the central nervous system or defect of nerve-vascular control which would cause capillary atony would produce a circulatory disparity resulting in the shock syndrome

Deficiency of Adrenal Cortex Recent experimental work (Swingle et al, Britton, Stewart and Rogoff, Banting and Garms, Hartman et al) on the adrenals indicates that one function of the adrenal cortex is to maintain venous and capillary tonus Animals deprived of the cortical hormone develop the characteristic manifestations of shock There are decreased blood volume, increased concentration of blood, low blood pressure, and an insufficient return of venous blood from the periphery There is transudation of plasma through the capillary walls Bloody vomitus and diarrhea are frequent Extreme weakness, prostration and coma precede death Many of the visible circulatory changes characteristic of shock are noted in the postmortem records, although none of the authors comment on

their significance. Apparently the lack of adrenal cortical hormone causes vascular atony with increased capillary permeability, and leads to death by a mechanism similar to that in shock from other causes. The circulation returns to normal, and may be maintained indefinitely, by injections of adrenal cortical extract.

The development of shock from lack of adrenal cortical hormone furnishes a significant illustration of the main thesis of this discussion. Increased volume-capacity of the vascular system, arising in this instance from a physiological deficiency, produces the typical shock syndrome. It is not probable that adrenal cortical insufficiency is an important factor in clinical cases manifesting the shock syndrome. I have not found visible evidences of adrenal abnormality in any human case or in experimental shock in animals. It would be of value to find whether adrenal cortical extract would restore the tonus of the minute vessels in shock arising from other causes.

Recently several writers (Parsons, Phemister, Blalock, et al.) have interpreted the shock syndrome as due entirely to loss of blood and fluid at the site of the trauma or injury. This mechanism obviously will not apply to all instances, such as those of shock following the injection of histamine, tissue extracts and various capillary poisons, the implantation of muscle substance in the peritoneal cavity, nor to shock developing from adrenal cortical insufficiency. In such cases there has been no local loss of blood or plasma. The authors have also overlooked the fact that, even where considerable local loss of fluid has occurred, the postmortem examination shows systemic vascular atony especially of capillaries and venules. Obviously any loss of fluid locally, as in extensive burns or physical trauma will contribute to the circulatory disparity, and its importance will be proportionate to the amount of blood and fluid lost.

It appears from the foregoing considerations that the shock syndrome results most frequently from dilatation of capillaries and venules plus leakage of plasma through capillary walls whose permeability has been increased. This feature has been present in shock produced by various means. It is a constant postmortem feature following shock from diverse causes. In the experiments which produced low blood pressure by simple vascular dilatation without capillary injury, shock did not result. A simple loss of blood or of plasma, the vascular walls remaining normal, does not progress but tends to restoration by physiologic processes. Fluid is absorbed from the tissues, or that supplied therapeutically is retained in the circulation. In shock the reverse is true. Fluid is neither absorbed nor retained and further loss by vomiting, diarrhea, effusion and by edema is progressive.

One concludes that increased capillary permeability is an essential factor in the mechanism by which shock progresses.

THE CLINICAL OCCURRENCE OF SHOCK

The rapid development of shock in a healthy person following extensive injury or surgery is a condition readily recognized. The gradual development of the same type of circulatory failure during some severe illness may not be recognized or may be attributed incorrectly to heart failure. Atchley discussed such cases as "medical shock" and cited instances in severe influenza, pneumonia and diabetic acidosis. He described the development of shock following an overdose of pneumococcal vaccine, and following a snake bite in which the venom apparently entered a vein. He attributed the circulatory failure to loss of capillary tonus, causing the vascular bed to become larger than the blood volume. He recommended the intravenous injection of hypertonic dextrose solution, of saline solution, and transfusion of blood as effective therapeutic measures.

Warfield recognized the development of shock in typhoid and other severe infections. He emphasized hemo-concentration as a feature and advised intravenous injection of fluids, or transfusions. He found such agents as strychnine, caffeine, adrenalin and pitressin of value but believed that digitalis was contraindicated, since cardiac weakness is not a factor.

Eppinger gave a comprehensive discussion of shock occurring under various conditions. He drew sharp distinctions between shock and heart failure. He emphasized hemo-concentration as an essential feature and explained it as due to leakage of plasma through atonic and permeable capillary walls. He reported cases of shock resulting from severe infections such as typhoid, cholera, scarlatina, pneumonia, peritonitis, and others, following poisoning with mercuric chloride, veronal, and other drugs, following meat poisoning, metabolic intoxications such as icterus, and following severe burns and other conditions. He indicated as appropriate therapeutic measures those which would stimulate the vasomotor center, those which would cause contraction of the peripheral vessels and of the blood reservoirs, those such as injections of fluid or transfusion of blood which would cause an actual increase in the blood volume, and those which by mechanical support, as abdominal binders, might facilitate a return of venous blood from the system.

Moon reported the occurrence of shock following burns, toxemias of various origin, poisoning with various substances, in severe acute infections, and in abdominal emergencies such as intestinal obstruction, hemorrhagic pancreatitis, mesenteric thrombosis, perforation or rupture of a viscus, etc. In each of these conditions the clinical signs of shock were present and in each there was marked hemo-concentration. At postmortem the findings corresponded exactly to the description already given. He emphasized that observations on hemo-concentration are of value in recognizing shock clinically and in estimating its severity.

A few details of the features present in some of these instances may be of interest. The typical clinical picture of shock develops following a severe superficial burn. The pulse is rapid and weak, the respirations rapid

and shallow, and the blood pressure declines progressively. Marked hemo-concentration takes place, as shown by red cell count, hemoglobin content and specific gravity of the blood. Thirst may be marked but water taken by mouth is not readily absorbed and is followed by vomiting of fluid containing blood. The temperature at first may be sharply elevated, but later becomes subnormal. The skin in areas remote from the burn becomes cold and clammy. Marked pulmonary congestion and edema develop. The urine becomes concentrated and often contains hemoglobin and albumin. Bloody diarrhea may be present. The mental state becomes clouded. Restlessness, delirium or coma may precede death.

The postmortem findings (Bardeen, Pack) are exactly those found in shock from other causes. They are identical to those described by Heubner and Dale following the injection of metallic salts or of histamine into animals.

Lewis and his associates have shown that histamine is a constituent of the normal skin, and that it is released in response to any type of injury to the cells. The local effect of this is to produce dilatation and increased permeability of the capillaries, resulting in congestion and edema. If a minute burn causes sufficient histamine to be released to affect the capillaries locally, the large amount released from extensive burns would produce similar capillary phenomena, systemic rather than local in distribution.

The degree of hemo-concentration following burns is proportional to the severity of the burn and to the degree of shock. Tappeiner (1881) reported four fatal cases of burns in which the erythrocytes ranged between 7,800,000 and 8,960,000. In five of Locke's 10 cases the erythrocytes reached 9,000,000. Underhill and his associates made blood studies in 20 cases of burns of varying degrees. In these the hemoglobin percentage ranged between 114 in the milder cases and 226 in the most severe.

I have reported elsewhere three cases illustrative of varying degrees of shock following burns. Three men were superficially burned following a collision in which a gasoline tank burst and ignited. The burns were of the second and third degree involving chiefly the legs, arms and faces. Shock was a marked clinical feature in each case. The burns varied somewhat as to the amount of skin involved, and likewise the degree of shock varied. The man having the most extensive burn had a red cell count of 8,350,000 and the hemoglobin was correspondingly high. He became semicomatose and died of circulatory failure within 48 hours. The post-mortem picture was that regularly found following burns or following shock from other causes.

Another man, burned at the same time but whose burns were slightly less extensive, died of secondary pneumonia 11 days later. His condition of moderate shock, as shown by blood pressure, blood concentration and general condition, continued during the 11 days. At postmortem the viscera showed the circulatory changes characteristic of shock or of burns. In addition to these, pneumonia of irregular type and distribution was

present. This feature is especially significant. Lungs whose circulation is impaired and whose spaces are filled with edematous fluid, present a stage already set for the final act—the development of pneumonia. This is probably the mechanism by which terminal pneumonia develops after severe burns.

The third man who was burned recovered. The blood concentration, shown in the following chart, declined gradually as the patient's condition progressed toward recovery.

TABLE I

| Date | Specific Gravity | Hgb | Red Cells |
|---------|------------------|-------|-----------|
| Dec. 14 | 1.075 | 120 + | 6,700,000 |
| " 15 | 1.070 | 112 | 5,400,000 |
| " 16 | 1.063 | 110 | 5,000,000 |
| " 17 | 1.070 | 116 | 5,200,000 |
| " 18 | 1.068 | 115 | 5,100,000 |
| " 19 | 1.066 | 110 | 4,990,000 |
| " 20 | 1.062 | 106 | 4,900,000 |
| " 21 | 1.055 | 99 | 4,630,000 |
| " 22 | 1.048 | 74 | 3,530,000 |
| " 24 | 1.045 | 87 | 3,820,000 |

The circulatory phenomena following burns are identical with those of histamine shock. The mechanism of origin apparently is not different from that of shock from other causes.

Drugs and Chemicals The characteristic features of shock occur in poisoning with various drugs. A man, aged 34, took an unknown amount of sedormide. Profound narcosis resulted and he was unconscious for 18 hours. On admission to the hospital the red cells were 6,030,000 and the hemoglobin 118 per cent. On the following day the temperature was 97°, the pulse 130 and the blood pressure 110 mm Hg systolic, and 70 diastolic. Adrenalin, atropine, caffeine and pituitrin were given as stimulants. Fluids were given by mouth, by hypodermoclysis and by glucose solution intravenously. These were ineffective. Death occurred within 72 hours. The postmortem findings were characteristic of shock as previously described. Bronchopneumonia in an early stage was also present.

Mercuric chloride poisoning frequently produces the shock syndrome. Such a case was reported by Moon and Crawford. A man, aged 39, swallowed 175 gr of mercuric chloride. The development of profound shock resulted fatally in 37 hours. Postmortem examination showed marked congestion and edema of the viscera, particularly of the pulmonary and gastrointestinal tracts. The lungs were markedly congested and engorged. Their combined weight was 1500 gm above normal, due to congestion and edema. About 1500 cc of blood-tinged fluid were present in the serous cavities. These two locations alone accounted for the loss of 3000 cc of fluid withdrawn from the circulation. Other organs were congested and edematous, capillary hemorrhages were numerous everywhere. This case illustrated strikingly the effects of severe, widespread injury to the capillaries.

The intravenous injection of arsenical compounds for therapeutic pur-

poses sometimes is followed by collapse ending in death. The postmortem findings in such cases are the same as in early death in mercuric chloride poisoning. Arsenical poisons are included among capillary poisons by Heubner, Kiogh and others.

Toxemias of Metabolic Origin Severe toxemias may result in circulatory collapse similar to traumatic shock. The following case is an instance.

A white man, aged 41, had a history of progressively deepening icterus, nausea, vomiting, clay-colored stools, weakness and malaise. The clinical diagnosis was acute yellow atrophy of the liver. On the day following admission the blood pressure was 106 mm Hg systolic and 60 diastolic, two days later it was 100 systolic and 56 diastolic. The decline in blood pressure was accompanied by a rise in erythrocytes from 4,490,000 to 6,240,000 and of hemoglobin from 81 to 110. Pulmonary edema developed which did not respond to atropine, but increased progressively. The pulse became rapid and weak. Glucose solution given intravenously at intervals caused slight temporary increase in blood pressure. Coma, a declining temperature and failing circulation preceded death. The postmortem examination showed acute hepatic necrosis and the circulatory changes characteristic of shock.

Toxemia associated with pregnancy may produce the shock syndrome. The following case is an instance. A white woman, five months' pregnant, became ill and was brought to the hospital. She had repeated severe convulsions, was very restless in the intervals, had constant thirst and dyspnea. The blood pressure was 220 mm Hg systolic and 180 diastolic when the patient was first examined. The pulse became rapid, weak and irregular. The lungs became congested and gave signs of edema. The blood pressure declined rapidly, and extreme prostration developed. The administration of caffeine, atropine, strychnine and the inhalation of oxygen were ineffective. Deep cyanosis and coma preceded death. At postmortem the circulatory findings were the same as in each of the conditions previously described.

In cases of eclampsia, of acute obstructive jaundice and of diabetic acidosis, terminating with clinical evidences of circulatory failure, I have found the same visible evidences of capillary atony.

Abdominal Emergencies Several grave pathologic conditions arising within the abdomen produce the shock syndrome characteristically. One of these is acute pancreatitis. A young woman suffering from acute hemorrhagic pancreatitis entered the hospital. She had a rapid weak pulse, rapid respirations, cold pale skin and falling blood pressure. No operation was done, the treatment was entirely symptomatic, she died of circulatory failure within 48 hours. Only one blood count was made. The red cells were 6,400,000 and the hemoglobin 112. At postmortem the visible evidences of shock were present in characteristic form. De Takats and Mackenzie reported nine cases of hemorrhagic pancreatitis, in all of which the red cells

were above five million and the hemoglobin correspondingly high. One case had 8,300,000 red cells and 140 per cent hemoglobin. They recognized the shock syndrome in each case and stated that blood counts furnished a means for determining the degree of shock.

Several authors have interpreted the syndrome which follows acute intestinal obstruction as shock. Yet the cause for death in this condition is still a much debated question among surgeons (Cooper, for review). That the essential clinical features of shock develop following volvulus or strangulation will not be questioned. I have recently reviewed the postmortem data on 26 cases in which intestinal obstruction was a feature. The majority of these examinations were made in the period before the gross and microscopic changes characteristic of shock were recognized. But in all cases such features as congestion and edema of the lungs and other viscera, effusion into serous cavities and petechial hemorrhages were noted.

We made experimental high intestinal obstructions in four dogs to secure further evidence on this point. In each instance the characteristic shock syndrome accompanied by hemo-concentration developed. And in each instance the gross and microscopic evidences were of the same character as previously described.

A similar development may follow severe trauma to the abdomen without penetration of the abdominal wall. Mesenteric thrombosis, and perforation or rupture of the abdominal viscera may produce shock. In each of these instances postmortem examination has shown the same visible circulatory changes as described before. It appears that substances producing capillary atony are derived from the bowel tract more readily than from some other areas. Surgeons have observed that shock frequently develops following abdominal operations which have required much handling of the intestines.

Infections. Many authors have noted the shock syndrome in acute infections. It is well known that cholera and gas bacillus infection develop into shock. Such observations coupled with experimental evidence indicate that bacterial products and substances derived from infected tissue may abolish capillary tonus as do other capillary poisons. My curiosity concerning the shock syndrome was first aroused during the pandemic of influenza in 1918-1919. Observations were made then which were not interpreted satisfactorily until recently. Many of the most severe cases died within two or three days of the onset. A few died within 24 hours. These rapidly fatal cases died of circulatory failure which the clinicians termed collapse or shock. Red cell counts in such cases ranged from 6,000,000 to 8,000,000 and the hemoglobin was correspondingly high. The clinicians soon recognized this as a grave prognostic sign. In such cases congestion and edema of the lungs developed rapidly and death resulted. Postmortem examinations showed wet bloody lungs and extreme capillary congestion of the mucosae of the pulmonary and gastrointestinal tracts. Frequently there was an effusion of reddish fluid in the serous cavities. No pneumonia

was present in these fulminating cases. The gross and microscopic features were indistinguishable from those following severe burns or following shock from other causes, as was learned later.

Underhill and Ringer made blood studies in 43 cases of influenza. In severe cases there was marked concentration of the blood, with hemoglobin values ranging from 110 to 140. Death resulted in each such instance. No hemo-concentration was found in the milder cases, and there was no instance of it among any patients who recovered. They concluded that the degree of hemo-concentration was an index of the severity of the illness and that it was of value in prognosis. Their description of the postmortem findings in fulminating cases agrees with those regularly found in such cases. These descriptions will apply with equal accuracy to the organs following death from burns. Neither Underhill and Ringer, nor any other author I have found, suggested a relationship between the circulatory changes described and the mechanism of circulatory failure which caused the death.

PNEUMONIA FOLLOWING SHOCK

In influenza of somewhat less severity the patients lived from seven to 15 days. Congestion and edema were marked but were not so extreme as in those who died early. The lungs were wet and bloody, and pneumonia of very irregular type and distribution was present. Bacteriologic studies gave no consistent results. Various organisms which are common invaders of the respiratory tract were found. Mixed infections were the rule. The gross and microscopic features were indistinguishable from those of secondary pneumonia following burns.

I have compared the gross and microscopic features of pneumonia following influenza, burns, surgical operation, intoxications of various kinds, and severe acute infections. I find no essential differences in their morphologic features nor in the bacteria which are associated. I believe that the same mechanism is operative in each of these groups of cases. It must be emphasized that the shock syndrome occurs in varying degrees and with varying rapidity. Shock of moderate degree and gradual development is of frequent occurrence. It is accompanied by pulmonary congestion and edema, and leads to death by secondary pneumonia. In material from 100 autopsies on adults, secondary pneumonia of this type occurred in 16 cases. Eight cases occurred following surgical procedures and one case each occurred in the following conditions: ulcerative colitis, acute hemorrhagic pancreatitis, drug poisoning (sedormide), obstructive jaundice, eclampsia, superficial burn of skin, diabetes with acidosis, and peritonitis. These presented the same type of pneumonia and were preceded by pulmonary congestion and edema in each case.

SUMMARY

The shock syndrome results whenever the volume of blood inadequately fills the vascular system. This may result from loss of blood or fluid, or from atony or dilatation of the vascular walls especially the capillaries and venules. Combinations of these two factors are the rule.

Circulatory failure of this type results not from cardiac or vasomotor inefficiency, but from an inadequate return of venous blood from systemic areas.

Increased concentration of the blood is a constant feature of shock. This is of clinical value both in recognizing the condition and in determining its degree.

Shock produces characteristic changes demonstrable by postmortem examination. These consist of marked capillary and venous congestion of the viscera, edema of lungs and mucosae, petechial hemorrhages in serous and mucous surfaces, and effusion of fluid into serous cavities.

Shock occurs not only following extensive surgery or trauma. It is seen in a wide variety of clinical conditions including extensive burns, poisoning with various substances, metabolic intoxications, abdominal emergencies and severe acute infections.

Cerebral hemorrhage and other lesions of the central nervous system may terminate in shock, the mechanism of which is not evident. Perhaps prolonged vasomotor disturbance results in tissue asphyxia which in turn causes capillary atony and permeability.

Shock develops in varying degrees. Maximal degrees lead to death by circulatory failure. Lesser degrees may be followed by recovery or by death from pneumonia.

Many cases of secondary pneumonia have their origin in this type of circulatory disturbance.

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ATOPIC ANNOYANCES IN THE COURSE OF PULMONARY TUBERCULOSIS¹

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THE word "atopic" is used in this paper to characterize spontaneous acquired sensitization to a foreign protein. This is an extension of Coca's¹ definition, but "allergy" means one thing to the allergist, another to the immunologist. For the purpose of the present discussion it is desirable to employ a term that excludes the delayed inflammatory reaction of the infected individual to tuberculo-protein, a reaction which students of tuberculosis generally describe as "allergic."

Atopic manifestations, especially hay fever, are often seen in cases of pulmonary tuberculosis. In 1925 I recorded the study,² from the viewpoint of the allergist, of a series of tuberculosis patients with asthma, and the following year reported the relief of hay fever by intradermal injections of pollen extract during the attack, commenting on the suitability of this method for tuberculosis patients because of the low dosage employed. Three years ago, the better to determine the frequency and importance of atopic complications in tuberculosis, I began to make, as part of the examination of all patients in a small sanatorium near Phoenix, a careful investigation as to the presence of sensitivity. This investigation included a detailed personal and family history, daily observation, and serial blood counts with particular attention to eosinophilia. When suspicious symptoms occurred the patient was skin tested, when indicated, desensitization was undertaken, the diet was modified, and the effect of adrenalin was tried. More recently residence in an allergen-free room has been used to aid diagnosis in doubtful cases. Because of the prolonged observation and control of the patients incident to their hospitalization for tuberculosis, it has been possible to establish in most cases whether or not the presenting symptoms were atopic in their origin.

The clinical material studied was that usual to sanatoriums in the Southwest: adults of both sexes, most of them with chronic tuberculosis, 70 per cent of them far advanced. They had the accepted institutional care, with considerable emphasis on rest, comfortable quarters, ample food, and a rather high incidence of intervention, especially artificial pneumothorax. In the mild climate of this region they lived out-of-doors 12 months of the year. Their average sanatorium residence was 8-1/3 months, but because some were old patients when this study was undertaken, and because of the follow-up system employed, their period of observation varies from four months to four years, and averages nearly two years.

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From St. Luke's Home, Phoenix, Arizona

Two hundred and fifty consecutive tuberculosis patients are included in this study. Fifty patients, one-fifth of the total number, showed during the period of observation clinically evident sensitization to identified foreign proteins. Four others had symptoms quite as typical, but their atopenses could be demonstrated only by the therapeutic test.

Sensitivity to Pollens In 34 cases sensitization to pollens was indicated by skin tests, confirmed by the effect of pollen therapy, and in certain instances further substantiated by the relief afforded by residence in the filtered air of an allergen-free room.

Sixteen of these patients had ordinary hay fever, with or without pollen asthma. Their ailment was easily controlled by intradermal pollen therapy and it did not perceptibly affect the symptoms or the course of their tuberculosis. But the remaining 18 of the pollen-sensitive presented a quite different picture, one that would hardly have been recognized for what it was without special study. Their nasal and conjunctival symptoms were slight, distinct asthmatic seizures did not occur. Instead, their pollenosis expressed itself by increased cough, increased expectoration with thin frothy sputum, and malaise. Some patients, during these apparent exacerbations, had elevation of temperature a degree or more above their usual normal. Examination of the chest showed a marked increase in moisture, not only over the bases but over the areas of heavier involvement. Piping râles and wheezing breath sounds were heard in most cases.

Chest roentgenograms, however, failed to reveal any unfavorable change, and the blood picture remained about as usual, except that the eosinophiles were increased. That such episodes were caused, not by colds or by localized extensions of tuberculosis, but rather by atypical manifestations of pollen sensitivity, was further shown by the fact that they were coincident with exposure to the offending pollens, the local reactions to the intradermal injection of the implicated pollens were unmistakably positive, and such therapy was followed by prompt relief. These atypical pollen patients showed a lesser degree of skin sensitization than was present in those with typical hay fever, and they required a somewhat larger dosage, over a longer period of time. It is of interest that this same type of clinical reaction to pollen occurred repeatedly in those individuals who were subject to it, either in a later season or when for some reason pollen therapy was stopped too soon.

The mechanism of these atypical pollen responses seems to be that of a mild continuous asthma acting on bronchi damaged by tuberculosis. In most cases the systemic effect, if any, was limited to a temporary loss of weight and impairment of the general health. In three instances, however, the pollenosis had gone untreated for some time, and it may have been related to the relapses which followed. It is reasonable to suppose that disturbed rest, increased lung symptoms, and worry over these untoward developments would in time impair the body's resistance to the progress of tuberculous disease. The case history now presented illustrates some of

the points mentioned, as well as the advantage of knowing, before they become clinically manifest, the sensitizations of a tuberculosis patient

Case 1 J C, male, aged 31 His mother suffers from hay fever and migraine, he himself was subject to ragweed hay fever and "sinus trouble" in Chicago for several years In 1931, as shown by films of that date, he had tuberculosis involving chiefly the right upper lobe After a year in a sanatorium he was discharged as arrested, and went to work He remained well until the fall of 1933, when he had an attack of what he thought was sinus trouble, he coughed considerably, wheezed a little, and lost weight He must have had active tuberculosis at that time, for when he came to Arizona and entered St Luke's Home in November 1933 he had well marked active disease in the right lung, with positive sputum, and the usual constitutional symptoms His skin tests at that time showed reactions not only to Eastern ragweed, but to all the local members of the ragweed group

An expansive pneumothorax was induced, and the patient became free from symptoms, except for a scanty sputum which was negative and remained so In March, with the pollination of *Franseria deltoidea*, he began to cough, and his sputum increased to nearly 2 ounces (50 cc) His eosinophile cells rose from 80 to 820 per cu mm Under treatment with the pollen of *Franseria deltoidea* all his symptoms subsided In June he was moved to the mountains for the summer and there in August he encountered the pollens of *Ambrosia psilostachya* and *Franseria acanthocarpa* His symptoms returned as before, and again subsided promptly under appropriate therapy In October he returned to Phoenix and there was exposed to the pollen of false ragweed, *Franseria tenuifolia* The same experience was repeated, at this time his eosinophiles rose from zero to 402 and dropped again as tolerance was established by intradermal therapy with the specific pollen None of these episodes interfered with his treatment for tuberculosis His course, as measured by clinical and laboratory standards, was continuously favorable

Sensitivity to Foods Sixteen patients were found to be sensitive to foods alone, and seven of the pollen-sensitive group reacted to foods as well The commonest manifestations of food sensitivity were those so familiar to the sanatorium worker complaints of "gas in the stomach," belching, a sense of fullness and distress coming on soon after meals, constipation of the spastic type, in three cases only, vomiting and severe pain Headaches of the migraine type were second in frequency, asthma, in definite attacks, was third Urticaria and eczema were seen a few times, vasomotor rhinitis from an identified food only twice

In diagnosing these food sensitivities and separating them from the digestive disturbances incident on the one hand to the toxemia of tuberculosis, and on the other to organic disease (usually tuberculosis) of the gastrointestinal tract, skin tests were useful in about half of the cases When all food tests were negative and the symptoms still pointed to sensitization, trial diets were employed for diagnosis These diets, patterned after those of Rowe³ but enriched by the addition of foods which the patient had seldom or never eaten, were highly effective in the difficult cases, not only in diagnosis but in treatment

As is not uncommon, the symptoms set up by food sensitivity in two cases simulated those of non-tuberculous disease within the abdomen In one, the picture was almost that of recurrent appendicitis except that the

blood examination revealed, instead of a leukocytosis, a normal white count with an eosinophilia. Another patient had for a year before admission been treated for cholecystitis. The barium meal with visualization of the gall-bladder showed no abnormality, and the symptoms ceased when wheat was excluded from the diet.

Even the barium meal was misleading in the following case, cited because one of its roentgenograms, reproduced in figure 1, constitutes one of the few existing photographic records of edematous lesions of the gastric mucosa caused by an identified atopen.

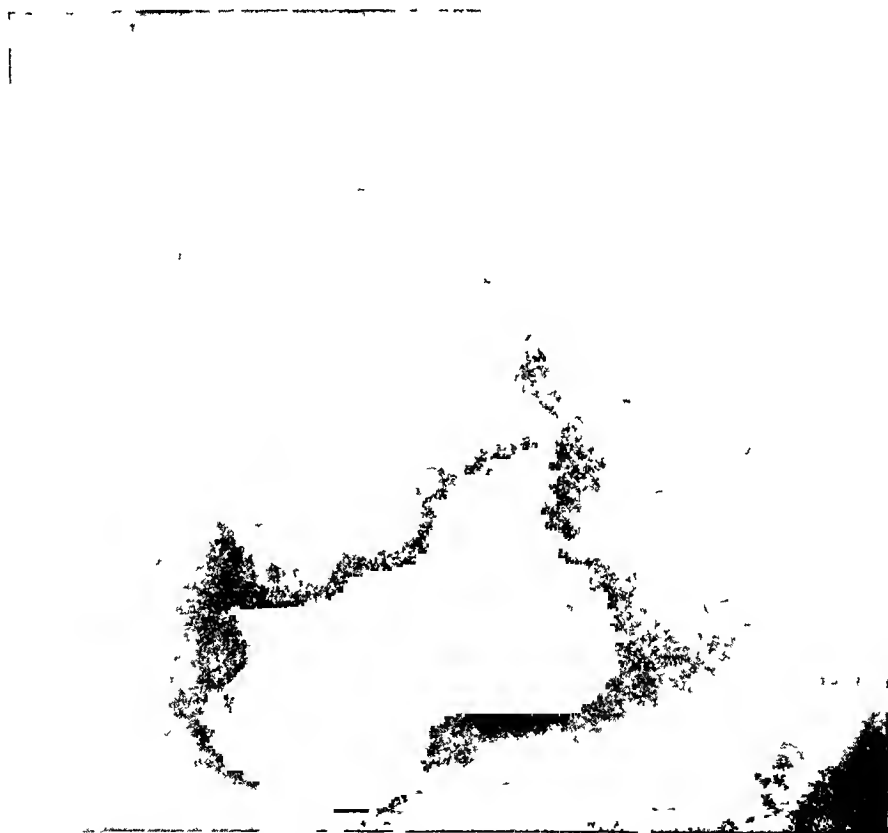


FIG 1 Roentgen-ray of stomach showing filling defects due probably to edematous areas in the gastric mucosa, atopic in origin

Case 2 F S, a young married woman, never pregnant, was admitted for the treatment of fairly recent tuberculosis of moderate extent. She was questioned in detail as to the presence of atopic disease in her family, and denied it. She said her own health had always been good, except for constipation. She was put on routine rest, and cod liver oil in tomato juice was ordered.

The girl was homesick, and she disliked the restrictions of the rest cure. After a week she began to vomit all her meals. For a few days she did fairly well on a diet of broth, milk, and carbonated water. Then her vomiting recurred, and with it violent abdominal pain, and retching. She could keep nothing on her stomach,

spasms of pain and retching kept her awake at night. All the usual palliative medication, including sedatives, and belladonna to its physiologic effect, was tried without relief.

Her temperature was normal, her urine negative. A surgical consultant found no evidence of organic disease. A gastro-enterologist after careful examination was forced to the conclusion that a gastric neurosis was responsible for her symptoms. He ordered bromides and normal salt solution by rectum, with nothing but cracked ice by mouth, for two days. During those two days she was quiet, but when oral feeding was resumed her symptoms returned. Her condition was alarming, and her family was notified.

After several trials a barium meal was retained and the roentgenologist, Dr. W. W. Watkins, reported: "At the six-hour period the patient shows stomach incompletely emptied, with areas of filling defect. If these areas are not due to food taken into the stomach, they should call for a reexamination. Two days later this was done, with the patient under constant observation to see that she took no food. The filling defects were again seen, and the report was: 'We have reexamined this patient, watching the barium enter the stomach with the patient standing. There are definite areas of filling defect which gradually disappear as the stomach partly fills with the barium mixture. These filling defects we believe were due to intragastric changes in the lining membrane of the stomach, probably polyps'."

Then the family arrived, and it was learned that the patient's mother suffered from migraine and her two brothers had hay fever. It was recalled that her blood count, a few days after admission, had shown 3 per cent of eosinophiles—a hint that mercifully had been ignored. Skin tests were done, and they revealed positive reactions to several foods, the strongest being tomato. Feeding was cautiously resumed with the implicated foods excluded. There was no further trouble, and the patient's subsequent course was uneventful. The roentgenographic picture three weeks later showed a normal stomach.

The offending foods were oftenest those which the patients had taken in excess in the hope of gaining weight: milk and egg, of course, cocoa, from the chocolate-flavored drinks advertised as body-builders, and tomato, from the vogue of tomato juice as a vehicle for cod liver oil. As in any series of food sensitizations, wheat, potato and chicken often reacted positively. Implicated foods were excluded from the diet until relief occurred, then, in most cases, they were fed again, one at a time, before being permanently forbidden. Sometimes in a multiple-sensitized patient a certain food, tried in this way, would cause the recurrence of one symptom only and not the symptom-complex from which the patient formerly suffered. In the case of C. McD., for example, the addition of milk to the diet brought back the headaches to which she had been subject, the feeding of eggs caused asthma, wheat and white potato produced digestive disturbances, mild continuous wheezing and nasal congestion. When all these foods were eliminated from her diet the patient gained weight, and felt better than she had for years. Recently, after two years of abstinence from these foods, she tried them again, one at a time, and they had the same effect as formerly, this notwithstanding the fact that in the interval her tuberculosis had become arrested and she was leading a normal life at the time of the second experiment.

The four cases whose atopens could be identified only indirectly, al-

though they received a disproportionate amount of attention, may be disposed of quite briefly. All four had eosinophilia, a positive family history, and negative skin tests. One patient had vasomotor rhinitis and mild asthma, relieved by a staphylococcus filtrate. Another had intense and intractable asthma which disappeared, not to return up to the present (18 months), following the injection of a few doses of antuitrin. In both cases the treatment was probably nonspecific. The third, with persistent asthma, was relieved only while in the allergen-free room. It has not been possible to find the offending inhalant, and this patient has had no relief. The fourth, who suffered from classical migraine that had continued unaffected by all the usual methods of attack, experienced complete relief after six infected teeth were removed.

Eosinophilia and the Family History An eosinophile count exceeding 2 per cent, and ranging from that up to 21 per cent, occurred in 32 of the 54 cases showing clinical evidence of sensitivity, it was present in only 27 of the remaining 196 cases, and one of these 27 has lately developed hay fever.

A family history of atopic disease was present in 32 of the 54 cases showing sensitivity, and in only 14 of the remaining 196 cases. Of this group of 14, one patient later died in an asthmatic seizure, two others developed hay fever.

The combination of positive family history and eosinophilia occurred in 23 of the 54 atopics, and only six times in the remaining 196 cases. Of these six, one now has orris coryza, and two children of another are asthmatic. It is clear that in this group of chronic tuberculosis patients the occurrence of eosinophilia (higher during exposure to the offending protein), the history of a familial trend to sensitivity, and still more the combination of the two, were of value in pointing to the probability of sensitization to foreign protein.

COMMENT

Estimates of the frequency of occurrence of atopic manifestations among the general populace vary all the way from the conventional "about 1 per cent" to Rowe's³ estimate of 35 per cent in a group of 400 university students, and Vaughan's⁴ appraisal, also based on anamnestic data, of 10 per cent of major allergy and 50 per cent of minor allergy in a group of 508 persons. That sensitivity to foreign proteins, especially to pollens, occurs often among tuberculosis patients in the Southwest has been noted by several workers in that region, including the writer. Sherman and Egbert⁵ in a recent publication comment upon it, and attempt to explain its mechanism. Their thesis, if I understand it, is that the constant absorption of tuberculo-toxin produces in the patient not only a relative immunity thereto, but also an allergic or "supra-allergic" state, in which sensitivity to foreign protein is more readily acquired. Quoting from their paper, "If we consider this

condition as the assimilation of a foreign protein into the tissue cells in such a state that the cellular activity is impaired with resulting edema then the so-called allergic individual may exhibit his symptoms in numerous devious ways. Too, once a patient exhibits any of these phenomena his blood-plasma is so changed that he soon acquires other foreign proteins which acquisition may progress until the original inciting cause is lost in a maze of allergic symptoms."

It seems unnecessary to venture so far afield to find an explanation for the prevalence of acquired sensitizations among the tuberculous, not in this series, at any rate. Most of the patients had chronic tuberculosis, all were on the rest cure, and they spent nearly all of their time in the open air. And in the region in which they were living, as I have shown in earlier publications,⁶ exposure to pollen is considerable. Fertile soil, a warm dry climate and abundant irrigation favor a rank vegetation, much of which is wind pollinated. There is little rain, and pollen remains a long time in the air and still longer in the dust. The pollinating season is nine months long, and in protected places plants bloom sparingly in the three remaining months. With so adequate an exposure it is not surprising that patients who have inherited the capacity to become sensitive to inhaled protein-bearing particles should develop pollenosis. But the pollen burden of the air in the Southwest, as shown by Durham's surveys, is less than that which occurs in the eastern and central states during the hay fever seasons—the very months when tuberculosis patients are most in the open air. It may be that careful investigation among such patients would reveal unsuspected cases of pollenosis, especially of the atypical sort described earlier in this report.

An equally simple reason for the prevalence of food sensitivity among tuberculosis patients suggests itself. The chronic chest patient leads a monotonous life. Food becomes a major interest, meal time an event in his day. Desiring to gain weight, he tends to overeat, and, since more than he can eat is set before him, he consumes in excess those foods which he likes or which he believes are good for him. His digestive powers being weakened by the enforced lack of exercise, probably at times he absorbs unchanged the proteins of his favorite foods. Under such conditions the mechanism of sensitization is rather obvious.

The present study does not corroborate the finding of Sherman and Egbert that "acquired allergy is most prevalent in arresting cases of tuberculosis, in which the immunity is greatest." All but nine of the 54 patients with clinical manifestations of sensitivity had active tuberculosis and positive sputum at the time their atopic symptoms were diagnosed. Several others (four, to be exact), as previously noted, developed sensitizations later in their course, and three of these still had active tuberculosis. But at least as many others lost their clinical reaction to foreign protein while their tuberculosis was healing, which is what occurs in any group of atopic persons, whether sound or tuberculous, if they receive appropriate

treatment It is suggested that if in a group of tuberculosis patients acquired allergy (in the limited sense) is found oftenest among those with healed or healing disease, it is because such patients have been longer on the best cure, and so longer exposed to some particular foreign protein

While the effect of sensitization episodes on the clinical course of tuberculosis varied with the reaction-type, they all had one feature in common—discomfort In chronic cases of the sort here considered, with extensive disease and many conditions influencing the physical state, one hesitates to evaluate precisely the effect of intercurrent ailments, or of their treatment Of the pollen cases in general it can be said that, following the control of their pollenosis by adequate therapy, they were more comfortable and felt better While I have seen a few cases in which the larger doses of a pre-seasonal pollen course produced a tuberculin-like effect in the presence of active tuberculosis, this has not occurred when the low dosage intradermal method was used This statement includes the one patient of this series who had a sharp constitutional reaction ("pollen shock") early in her treatment Lichtenstein⁸ even administered pollen extract intravenously to a consumptive without apparent detriment Sherman and Egbert find that desensitization of a tuberculous individual to an offending protein is harmless It may be said that it is worth while to protect the tuberculous invalid against the discomforts of pollenosis of either type Such desensitization is safer than to permit the pollenosis, with its attendant risk of sinus infection, to continue, and it can be accomplished as well during the attack as at any other time, if the proper methods are used

Sensitivity to foods caused not only discomfort but also some impairment of nutrition Not only patients whose symptoms were referred mainly to the digestive organs showed this effect, those with migraine and asthma lost weight when the seizures were frequent Correction of the diet in such cases was always beneficial to the general health, and to that extent at least it aided recovery from tuberculosis The working rule that restriction of diet should never be carried to the point where it caused a continuing loss of weight was found to be important If necessary, dextrose was used to add extra calories to the trial diets As a matter of fact, most of these patients gained weight when relieved of the distress caused by specifically offending foods

The study of so many individuals from the viewpoint of the allergist consumed considerable time, effort, and material, but considering the results obtained and the period of time over which these results were helpful to the patients concerned, the undertaking has seemed worth while, and worth continuing as a part of institutional routine Pollen-sensitized patients were relieved of discomfort which interfered with their rest Those sensitized to foods not only were made more comfortable, but their nutritional state was improved, a few were freed from disturbances which threatened the success of their entire treatment It is not suggested that work of this sort is a prime requisite in the successful treatment of tuberculosis, too

many have recovered without it. But, taking a comprehensive view of the measures at the disposal of the clinician, it may reasonably be asserted that informed attention to the diagnosis and treatment of sensitivity as it occurs among chronic tuberculosis patients will be helpful to a considerable number of these, and a useful addition to the hygienic treatment of tuberculosis.

SUMMARY AND CONCLUSIONS

1 Two hundred and fifty consecutive chronic tuberculosis patients were observed in an effort to determine the frequency and the effect of atopic disease among them. Fifty patients, one-fifth of the total, presented clinical evidence of sensitization to identified foreign proteins.

2 Thirty-four of these atopic patients were pollen-sensitive. About half of these had simple hay fever, easily controlled by specific therapy.

3 The remaining pollen-sensitive patients presented the atypical symptoms of increased cough and increased expectoration. These symptoms were likewise controlled by pollen therapy.

4 Sensitivity to foods alone occurred in about one-third of the atopic patients. Some of the pollen-sensitive reacted to foods as well.

5 The symptoms of food sensitivity resembled frequently the digestive disturbances incident to the toxemia of tuberculosis, less often, those caused by organic disease of the digestive tract. Both sorts were relieved by exclusion of the offending foods from the diet.

6 The discomfort incident to pollenosis interfered with the patients' rest and was detrimental to their general health. Food sensitivity, in addition to this, impaired their nutritional state.

7 In dealing with food sensitivity in tuberculous patients, the diet should not be restricted to the point of causing continued loss of weight.

8 Chronic tuberculosis patients on the rest cure, spending most of their days and nights in the open air, are heavily exposed to pollen in the pollinating seasons.

9 The same patients, leading a monotonous life and desiring to gain weight, are likely to eat in excess foods such as milk and egg, and tend to become sensitized thereto.

10 Appropriate pollen therapy, before or during the attack, may safely be employed in the presence of active tuberculosis.

11 The recognition and proper management of sensitivity to foreign proteins constitute a useful addition to the hygienic treatment of tuberculosis.

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PAIN—THE PATIENT'S COMPLAINT *

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PAIN is defined in Dorland's Medical Dictionary as "distress or suffering" The derivation of the word is from the Greek appellation for penalty Hence, in Webster's Dictionary, the first definition is given as "punishment, penalty, or fine," and its common usage as "an affection or feeling due to derangement of functions, disease or bodily injury," second, and "distressing uneasiness of mind, grief" is placed fourth

With consideration of the wider uses of the word "pain," practically all bodily and mental ills present attributes which may be included under this designation Pain is the most frequent complaint offered by the patient when he consults the physician With the wide scope allowed by the definition and the innumerable conditions which give rise to painful sensations the complaint obviously requires limitation and careful investigation

VARIETIES OF SENSATION DESIGNATED AS PAINFUL AND SOME MECHANISMS INVOLVED

Pain is a necessary part of an animal's mechanism of defense—the automatic danger signal But perception of painful stimuli varies greatly, for it is bound up with the patient's physiological functions and emotional stability Various areas and organs of the body do not respond equally and in the same manner to stimuli

Illustrative of this physiological difference Lennander and Mackenzie's investigations showed that viscera do not respond to the same character of stimuli that give pain in somatic structures, viscera could be cut, pinched and burned without pain, the nerves supplying them not having the same property of pain conduction Head established that the afferent visceral nerves were the same which furnished skeletal tissues with deep and protopathic sensibility In the absence of the inhibition of the higher centers an impulse might be transmitted to the thalamus and cortex where pain is not ascribed to the particular viscus in which the impulse arises, but is referred partly to the surface of the body, as segments or sections are represented centrally, just as in the cortical motor system, movements and not muscles are represented When painful visceral stimuli reach the perceptive brain centers the effect is regularly redistributed segmentally as definitely as motor and trophic distribution is accomplished in the cord Each viscus supply is from several segments, hence, the area of reference may be widespread as particularly pointed out by Pottenger Also Behan suggests impulses may travel up or down segmentally, before entering the central nervous system and then be reflected peripherally, giving referred pain Head's law

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also offers a further criterion. When a painful stimulus is applied to a part of low sensibility in close central connection with a part of much greater sensibility, the pain produced is felt in the part of higher sensibility.

As expressed in the definition, the complaint of pain does not preclude that a true physiological sensation of pain is present. The complaint called painful may result from irritation due to distention of a hollow viscus, from reflex spasm of a neighboring organ, may present itself peripherally as a tender or painful point or arise from innumerable stimuli. It may be expressed in any form of sensory appreciation, as an actual sense of pain, hyperalgesia, or hypalgesia, abnormal heat and cold sensation, irritative phenomena, felt as tingling, scratching, formication, gnawing, electric-like, a feeling of pressure, or weight pulling, stretching, soreness, aching, or any known sensory perception, its description usually being influenced by the patient's intelligence, experience and education.

Furthermore, differentiation between sensitiveness and tolerance must be made. Libman uses as a test for individual sensibility, pressure against the tip of the mastoid and then over the styloid process. He quotes Sir James Paget in that "pain expected, watched for, long thought of, will come" and calls attention to the recognition of the factor and effect of distraction. He also points out the existence of covered symptoms in the hyposensitive individual where pain is not predominant, as the dyspnea of coronary disease overshadowing precordial distress which might be marked in the absence of dyspnea.

In multiple foci of a disease, change of position allowing another pain point to cover one previously distressing, is a common observation. One condition of two different clinical entities may not be noted in the presence of one more distressing and important, as an arthritic pain in the presence of angina. Substitution symptoms occur frequently, as the complaint of fullness, pressure, gas, headache, etc., in the presence of gastric ulcer. Hyposensitive individuals may dread dental drilling more than extractions and in this type advanced neoplasms may give referred and substitution symptoms of "crowding," pressure and vague discomforts which must be magnified in estimation of the true condition.

In this general but great difference in the reactions to pain between the sensitive and hyposensitive, it appears that the impulses travel more directly to the central nervous system in the former while in the hyposensitive impulses seem to be delayed in the autonomic system.

Carnett refutes the viscerosensory reflex viewpoint, believing that much lower abdominal pain is parietal neuralgia which his skin pinch test will differentiate from intra-abdominal pathology and thus obviate much misdiagnosis and unnecessary abdominal surgery.

Physiological nerve function, though somewhat complex and confusing at times, is usually given appropriate consideration and study, but the role of neurotic tendencies and frank psychoneuroses in the causation of physical disability is not fully appreciated. Their presence and manifestations,

however, may be fully as distressing as any physical discomfort. All ailments and physical incapacities are influenced by the attitude of the patient toward them. When this attitude is dictated by an unstable emotional system, mental conflict and ungratified wish fulfillment, the symptoms presented are variable, confused, complicated and perplexing. Hence, routinely, this attitude must always be considered if one is to expect complete and rapid recovery from the condition present, and when the situation is complicated by the presence of a psychoneurosis it is extremely helpful and often necessary to evaluate its influence properly.

To best accomplish this, a workable understanding of the mechanisms involved in psychogenic symptom formation is as necessary as knowledge of the pathological and physiological processes involved.

Hysteria is the most protean and varied of mental disorders. Its psychology includes opposing wishes with accompanying mental conflict which often manifests itself in bizarre behavior in the attempt to influence spectators and auditors.

Frequently associated are sexual desires striving for satisfaction against opposing inhibitions of fear-dominated conscience. Usually conscience wins in the conflict but whatever the result disappointment and dissatisfaction ensue, leaving little chance for happiness in the hysteric. Usually emotionalism with temper outbursts appear or unconscious compromise by symptom development serves to gratify repressed desires by substitution or symbolism. These subconsciously motivated symptoms may take the form of a phobia, a tic, an illness or somatic reference to any organ or system. This may offer a solution for the mental conflict, but its subconscious motivation not being recognized, relief is sought for this very symptom which is the gratification of the consciously intolerable wish. The substitution in this way of physical symptoms for emotional problems constitutes "conversion hysteria." Here emotional energy instead of appearing in higher behavior levels as intellectual and mental activity seems to be resolved by the development of physical symptoms through neural transmission paths in the form of more obvious physical and motor manifestations. This mechanism is responsible for many of the minor disorders in general practice. The symptoms presented are probably not desired as such, either consciously or subconsciously, but they are purposive, in that they serve as a means towards the desired end or goal.

Economic hardships and social demands make wish fulfillment difficult to achieve. The liability to physical impairment is thus obviously increased, offering a very definite economic as well as medical problem, as shown by the development of increased incapacity in employees and in the insured and in a marked increase in the number of indigents requiring charitable aid.

Such somatic conversion of symptoms may involve any bodily organ but the genital and erotogenic zones are particularly prone to be the sites involved. Irrespective of the particular complaint offered in this condition the underlying mental conflict is usually quite obvious and causative of much painful distress.

Without proper supervision this distressed patient seeks aid promiscuously, frequently becoming the victim of quackery and of mercenary, unethical individuals who only more firmly fix his symptoms and, incidentally, usually relieve him of his available funds and assets. On the other hand he may be conscientiously treated by ethical and well trained physicians who are not sufficiently familiar with or cognizant of the syndrome or mechanism in the development of the bizarre unrelated manifestations which may be presented.

Patients with conversion symptoms are seen in all specialties of medical practice but due to the fact that the most frequent zone of reference is that of the sexual and neighboring organs, the gynecologist, urologist, gastroenterologist and proctologist are most likely to be sought for advice or treatment.

A few examples of symptoms developed in this condition demonstrate its mechanism.

Case 1 C Y, 30, bank clerk, contracted gonorrhea from the girl he had planned to marry, which offered more emotional distress than physical, for many months. However, about two years later he married another girl, who during her pregnancy which began the first month of their married life, was sick much of the time, had a very arduous and dangerous labor, and following the birth of the child gave it intensive attention with little to the husband. Fear of another pregnancy possibly further lessened her limited sexual desires, and gave the husband need for long continued repression. During this time economic stresses in the form of salary decreases and the wife's parents moving in with them, aided in the development of an anxiety neurosis. After a few weeks of intense worry and some emotionalism the patient developed a severe pain in the anal region relieved only by standing. He found himself unable to sit at his desk for more than a few minutes at a time and frequently at bedtime or during the night he was impelled to arise and gain relief by walking. He consulted an able urologist who treated him with prostatic massage and finally, as the symptoms did not abate, resorted to a prostatic median bar transurethral resection, which was also ineffectual. He was then advised to have a rectal examination in search for the causative source. A minor rectal operation was advised and accepted without relief. Meanwhile he had had several negative physical examinations and was found upon neurological examination to have no organic disease of the nervous system.

Case 2 J S, 43, electrician, was referred by a proctologist to whom the patient had been sent by a urologist, with an identical complaint of rectal pain. Their examinations disclosed no genito-urinary or rectal lesions. Only a few details in his long search for relief will be mentioned. At 19 he had contracted gonorrhea from which he quickly recovered but, thinking treatment should be continued, he left his parents' home and came several hundred miles to live in Los Angeles, among strangers and for a year continued unnecessary treatment with advertising specialists. Then called to army service he apparently adjusted well and obtained a good position upon discharge. Four years ago, however, rectal pain suddenly began and has continued since, causing much loss of sleep, inability to hold a position, psychic impotence with its attributes added to his anxiety and emotionalism, the treatment of which had dissipated his resources, due to his persistent search for relief. Throughout his trouble he received no examination or treatment from ethical physicians until examined last month by the urologist and proctologist mentioned. He spent \$750.00 for a goat gland bilateral testicular transplantation but the pain recurred promptly.

after the operation. He had also paid \$150 00, cash in advance, for glandular extract injections, and several hundreds more of his frugal savings with advertising "men's specialists."

Case 3 C W, 21, broker's clerk, was referred by a urologist who recognized his complaints of numbness of the penis, psychic impotence, extreme lassitude and apathy as psychogenic in origin. Subconsciously he had built on fear, shame and a feeling of inferiority following a gonorrheal infection over a year previously. A personality change from that of an active social individual, efficient in his work to one of inactivity, isolation, indolence, lack of interest, impaired integration and inability to concentrate had occurred. He avoided all his former friends and social gatherings but was retained in his position for a time, in spite of his attitude, by an understanding and patient superior.

Case 4 Mrs A C, 26, was referred by a urologist to whom she had been sent by a friend to discover if any physical reason existed for absence of sexual gratification at intercourse and persistent dysuria and frequency. Her entire girlhood had been embittered by the constant argument, harangue and bickering between her impatient, hypercritical, quarrelsome parents. After disappointment in a matrimonial engagement to a man near her age, she was much distressed and very emotional for over a year. Near the end of this period she became acquainted with a man almost 30 years her senior, who was very understanding and patient with her mental turmoil and distress. This man fulfilled the father ideal which she had entirely missed in her own father, as well as fitting the rôle of lover. Marriage ensued yet, despite frank discussion of both the physical and mental phases of sex in married life, physical difficulties and economic stress led to increasing marital estrangement.

Physically the patient was extremely well developed and likely oversexed. This, together with obvious failure of gratification, early in her married life, due to partial impotence in her husband, caused her the definite physical distress of unrelieved desire with increasing repugnance towards her husband. Psychic frigidity developed and conversion symptoms in the form of dysuria and frequency appeared. Divorce was seriously contemplated and extreme unhappiness was being experienced by an intelligent and otherwise cooperative and congenial couple.

Case 5 Mrs J S, 26, gave nearly an identical history except that she had married a man near her age. She had consulted a female osteopath who had attributed all her trouble to uterine retroversion. Many months' treatments with packs, pessaries and position exercises had but further increased the patient's dissatisfaction until the very presence of her husband brought on emotional episodes very disastrous to marital peace and happiness.

Case 6 Miss G, 28, a hard-working office woman, the sole support of her invalid mother, had lived an extremely restricted social life, giving all her time outside of working hours to the care and entertainment of a selfish, demanding and critical mother. A gastrointestinal upset caused her physician to suspect a mild attack of appendicitis.

Within the next two years similar attacks recurred every few weeks, which resulted several times in hospitalization, careful study and consultations. An element of exhibitionism being present also, the attention she received while ill brought no little satisfaction and gratification into her emotionally starved and limited existence.

Case 7 A 17-year-old high school boy was taken to the ophthalmologist because of rapidly failing vision. Vision was found to be 6/6 in each eye and no pathologic lesions were present except a mild traumatic *blepharitis marginalis*. The history was given that the boy had not resumed school four months previously at the opening of the session, apparently on account of his inability to see well enough to study. Upon examining the boy a first degree hypospadias was found present. Further investigation revealed that he had attempted to avoid his fellows and isolate himself, for

they were considered "normal," "able" and physically maturing as he was unable to do, completely, on account of his physical impairment. A feeling of inferiority, inadequacy, shame and much mental turmoil had developed. Subconsciously the conversion symptom most effectively removing him from his disturbing environment developed in the form of marked visual impairment. School attendance was obviated and association with his normal companions was much restricted.

In this situation much difficulty would be experienced by this patient in properly adapting himself, with the ideas he held regarding the extent of his physical inadequacy. Consequently a plastic operation was advised but the physical impairment and its attributes were minimized to him, awaiting the acceptance and results of the proposed operative procedure.

DIAGNOSIS OF PSYCHONEUROSIS

Similar conditions could be recited tiresomely. Daily, puzzling syndromes, complicated by the patients' emotional content or actual psychoneurotic manifestations, are presented to the examining physician. Frequently the underlying motives are obvious but at other times the psychic element is extremely difficult to evaluate. Whenever the subjective complaint is not accompanied by definite physical conditions and signs which might reasonably be the exciting causes, the social, economic and emotional states of the patient should be investigated. Rather than by a process of exclusion, however, the symptomatology of the psychoneuroses should be as readily recognized as that of other illnesses. There is usually present a demonstrably peculiar emotional state of abnormal suggestibility. There is frequently a tendency to blame the medicine prescribed or the therapeutic measures instituted for continuance or exacerbation of symptoms. Often this resentment is extended to the physician who has suggested the specific remedial agents and the tendency to blame anyone but himself for his condition, physical, economic, and social is usually present. The patient's past history usually evidences ineffectiveness in his personality, poor adaptation to his environment, inadequate handling of his personal problems, often disagreements with his confidantes and superiors, which may cause frequent changes in positions and abodes, social difficulties or marital infelicity and general maladaptation and frequent errors in basic judgment throughout his life. The elicitation of faulty thinking, mental conflict or unusual reactions must be given their proper degree of importance in the study of the patient and his complaint.

Furthermore, the psychic reactions to every illness or disability play an important part in its degree of incapacitation, progress and treatment.

The patient's sum of past experiences, economic and marital status, emotional stability, ease of adaptation to varying situations, personality type and degree of happiness at the time are but a few of the numerous contributing factors influencing this reaction. Hence, in the emotionally unstable, worrisome, highly suggestible individual, it is often more efficacious and productive of greater final good to minimize the effect and danger of benign, innocuous, nonprogressive conditions, or postpone their treatment,

if it can be done without risk, until the patient's mental turmoil, anxiety and introspection become lessened

TREATMENT

The treatment of an existing psychoneurosis consists principally in reeducation in a new attitude towards life and its problems. In an older resistive person whose opinions, thinking habits and reactions are fixed a real problem is presented but usually a better adjustment can be affected. Fundamentally the confidence of an introspective, egotistical, self-centered individual, in which type such conditions usually exist, must be gained. If practical, in the particular patient, explanation of the mental mechanisms in the development of his symptoms may be helpful. In a patient where this method would be inadvisable or poorly understood, material obvious agents, in the form of physical therapy and electrotherapy, may be helpful, using care they are not accepted as panaceas.

Tactful, indirect suggestion, encouragement, incentive for recovery and a better method of reaching desired goals need to be offered. A transfer and diffusion of interests will need to be developed by encouraging physical, intellectual and social activities, pointing out the obvious compensations that they offer.

Withal, a more philosophic and optimistic attitude must be promoted and methods of better adaptation demonstrated.

Neuropsychiatrists have been accused, at times, of being impractical, visionary and, what is still more important, of neglecting possible physical attributes in conditions presented for their investigation. Many medical practitioners, especially those in special work, are liable to become limited in their viewpoint. Fortunately these tendencies have been much lessened with the more intensive medical training in all basic branches of practice in school, hospital and graduate study. With the development of greatly broadened viewpoints generally, the neuropsychiatrist is able to point out to his confreres that the damage accruing from over enthusiastic, injudiciously applied, diagnostic and therapeutic measures may be as great in the suggestion and fixation of ideas and the development of a neurosis as their benefit may be obvious when they are indicated.

The value of considering the patient's reaction to his ailment cannot be overestimated. Consequently, knowledge helpful in the estimation of its effect and evaluation is as necessary as that regarding other investigative procedures. Palliative treatment may alleviate the acute distress by removing obvious physical evidences of discomfort and incapacity. However, when the symptoms are of psychogenic origin, or a condition is exaggerated, prolonged and made more materially incapacitating by the subconscious mental reaction towards the symptoms, an intensive reeducational procedure needs to be employed. With this accomplished the patient will learn to live the happy, contented existence to which he is entitled.

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THE ASSOCIATION OF POLYCYTHEMIA VERA AND PEPTIC ULCER ¹

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OUR interest was aroused in the significance of the association of duodenal ulcer and polycythemia vera as a result of observation of a patient who had both diseases. A review of the literature revealed interesting speculations in regard to the association of these conditions because of recent demonstrations of the relation of gastric secretion and hematopoietic function. It seemed reasonable that with the large amount of material available at this clinic some conclusions might be drawn as to the incidence of association of these diseases.

In the available medical textbooks, the gastrointestinal symptoms associated with polycythemia vera are minimized. Osler ¹ dismissed the subject with the simple statement, "Gastrointestinal symptoms are not prominent." Perhaps the most common manifestation referable to the alimentary tract of patients with polycythemia vera is constipation, which is variously described as being inconstant or common. The next most frequent abdominal symptom usually is distention or fullness, which is usually explained on a basis of pressure exerted by an enlarged spleen, it is sometimes accompanied by pain, which is often localized in the epigastrium or left upper quadrant of the abdomen. Nausea, vomiting, and anorexia occur quite frequently. Melena or hematemesis may occur, as may epistaxis, hematuria, menorrhagia, cerebral hemorrhage, or bleeding into the pleural cavity.

The first report of the association of the two diseases was in 1905, thirteen years after Vaquez ² described polycythemia vera. In that year Weber and Watson ³ reported observation of a patient who had polycythemia vera and who gave a history suggestive of peptic ulcer. At necropsy there was observed an intense congestion of the gastric mucosa and a round ulcer on the posterior surface of the stomach, 2 inches (5 cm.) from the pylorus. Schneider, ⁴ in 1907, reported the simultaneous occurrence of gastric ulcer and polycythemia vera. Giffin ⁵ has also noted the occasional association of peptic ulcer and polycythemia vera.

In 1913 Friedman ⁶ advanced the opinion that duodenal ulcer might be a trophic disorder due fundamentally to a disturbance in the secretion of epinephrine, which he suggested as the cause of the polycythemia in the cases he had observed. He stated that polycythemia is apparently a frequent finding in cases of duodenal ulcers that do not bleed, and that this is not true of gastric ulcers. In most of his cases the existence of duodenal ulcer had not been proved, and in many cases polycythemia was probably of

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a secondary or concentration type. In 1914 Friedman⁷ reported the occurrence of an elevated erythrocyte count in 13 of 16 cases of duodenal ulcer, and observed that the polycythemia continued after operation in those cases in which surgical treatment was undertaken.

Naegeli,⁸ in 1919, mentioned pyloric ulcer with obstruction as a cause of relative or concentration polycythemia. Buig,⁹ in 1920, reported two cases of duodenal ulcer associated with polycythemia, and stated that Danish writers had observed four similar cases. He was of the opinion that the polycythemia was a result of three factors: gastric hypersecretion, delayed passage of food from the stomach, and dehydration from frequent vomiting. Hirschfeld,¹⁰ in 1925, stated that the polycythemia which may be observed in pyloric stenosis occurs as a result of lessened fluid absorption.

Tuchfeld,¹¹ in 1931, observed that patients with pyloric or duodenal ulcers frequently have an associated, abnormally high erythrocyte count and hemoglobin value. He contrasted the anacidity associated with pernicious anemia with the hyperacidity observed in these cases of duodenal ulcer and polycythemia. He suggested that in the latter cases there is an excessive production of that component of the gastric secretion which is concerned with the formation of erythrocytes. Morris,¹² who named the hematopoietic factor of the gastric juice "addisin," suggested in 1933, as had Tuchfeld¹¹ previously, that in polycythemia there might be produced an excessive amount of this factor, in contrast to the lack of its production in pernicious anemia. He advised a patient who had polycythemia and a duodenal ulcer to lavage his stomach three or four nights a week for a period of six months. During that period the erythrocyte count dropped from 10,000,000 to 5,300,000 per cubic millimeter. When lavage was discontinued, the count again rose to 10,200,000. Recently, Oerting and Briggs¹³ reported a favorable influence of gastric lavage on "familial and nonfamilial erythremia." These observers found, in addition, that the gastric secretions of patients with polycythemia were capable of producing remissions when placed untreated in the stomachs of patients with pernicious anemia.

Boyd,¹⁴ in 1934, reported the simultaneous occurrence of polycythemia, leukocytosis, and duodenal ulcer. He called attention to the known tendency to thrombosis often observed in polycythemia vera, and offered the opinion that the duodenal ulcer was probably secondary to thrombosis in the duodenum.

Not all writers have been able to concur in the opinion that duodenal ulcer and polycythemia are frequently associated. Allodi and Griva,¹⁵ in 1930, reported 63 cases of ulcerating or nonulcerating affections of the duodenum, or other sections of the intestine, accompanied by hyperchlorhydria. In only two cases was there actual elevation of the erythrocyte count.

It is important to recognize that some of the cases reported in the literature as polycythemia vera probably should not be classified as such in the absence of more definite criteria of the disease. Undoubtedly some of these patients presented concentration polycythemias or polycythemic hypovolemia,

and one must be cautious, therefore, in drawing too many conclusions from reports in the literature. The reports of several authors have raised interesting speculations as to the etiologic relationship between polycythemia vera and ulcer. It has been suggested that both diseases are a result of disturbance in the secretion of epinephrine, that polycythemia is relative or secondary to loss of fluid, that duodenal ulcer, being associated with hypersecretion, results in an excessive production of an intrinsic erythropoietic factor, and that the occurrence of ulcer is the result of thrombosis of vessels in the gastric or duodenal mucosa.

CASES STUDIED

We investigated 143 cases of proved polycythemia vera at The Mayo Clinic for the purpose of determining the frequency of associated peptic ulcer. The diagnosis of polycythemia vera was made in these cases on the basis of elevation of the erythrocyte count and hemoglobin content above normal values, increase in viscosity and volume of the blood, and a hematocrit reading indicating a higher percentage of erythrocytes than the normal value of 45 to 48 per cent. Many of the patients were observed over a considerable period, as they were under treatment with phenylhydrazine (Brown and Giffin,¹⁶ Giffin and Allen¹⁷) and consequently the opportunity for detecting gastrointestinal symptoms was great. Of the patients, 114 gave no history suggesting the presence of gastrointestinal disease, and therefore had no roentgenologic examination. In 17 cases roentgenologic examination of the stomach and duodenum did not reveal any pathologic process, in 12 cases, or 8 per cent, there was roentgenologic or pathologic evidence of the presence of peptic ulcer.

In 10 of the cases of ulcer the lesion was in the duodenum, in two in the stomach. In the group of cases of duodenal ulcer, the lesion was demonstrated by roentgenologic examination in nine cases, at postmortem examination in one. In two cases of this group there were no features in the history to suggest the presence of peptic ulcer, in seven cases the history of ulcer antedated the development of symptoms or discovery of polycythemia vera by at least one year and in one case by 21 years. In one case there was some question as to the sequence, but symptoms of polycythemia vera were probably noted before those of duodenal ulcer. Six of the patients had symptoms of duodenal ulcer at the time of examination.

Of the two patients with gastric ulcer, one gave no history suggestive of ulcer, and the lesion was an incidental finding at postmortem examination. The other patient had symptoms of ulcer for four years, and of polycythemia vera for slightly more than two years.

Studies of the acidity of the contents of the stomach of patients with polycythemia are worthy of note in view of the possibility of a relationship between gastric secretion and polycythemia. In only one of 24 cases in which gastric contents were studied was marked hyperchlorhydria present.

This patient had an active duodenal ulcer, and the value for free hydrochloric acid was 80 units and for total acids (Ewald meal) 96 units. Four other patients with active duodenal ulcer had acid values moderately above those considered to be normal. Sixteen patients had acid values within normal limits, and four either had no free hydrochloric acid or very low acid values. In none of the cases without ulcer was hyperchlorhydria present. Unfortunately, studies of pepsin content of the gastric juice have not been made in most of these cases. In one case of duodenal ulcer and polycythemia vera in which the gastric pepsin was estimated following stimulation with histamine, the values were above normal, and were commensurate with the degree of hyperacidity. In another case of polycythemia vera without gastric or duodenal ulcer the pepsin values were two or three times the normal.

COMMENT

There are two points of interest in regard to this problem: first, whether there is a significance in the association of duodenal or gastric ulcer and polycythemia vera, and, second, whether there is a relationship, as suggested by Tuchfeld¹¹ and by Morris,¹² between changes in the gastric juice and the elevated erythrocyte count.

The actual incidence of peptic ulcer in the general population is unknown; studies by pathologists suggest that healed or active ulcers are found at postmortem examination in 10 to 20 per cent of cases. Hartman¹⁸ reports that ulcer of the stomach or duodenum was found in 3.2 per cent of patients who registered at The Mayo Clinic in 1928. In a control series of 200 consecutive cases of hypertension, in which patients were examined in 1929, one of us¹⁹ found the incidence of gastric or duodenal ulcer to be 2 per cent. In contrast with these control groups, the present study indicates that in 8 per cent of cases of definite polycythemia vera there was roentgenologic or pathologic evidence of peptic ulcer. Since not all of the patients with polycythemia vera were investigated to determine the presence of ulcer, and since in a few of the cases there was roentgenologic or pathologic evidence of the ulcer in the absence of symptoms suggesting ulcer, it is impossible to state accurately the exact percentage of association. While a duodenal or gastric ulcer was recognized more frequently in cases of polycythemia vera than in a control series consisting of patients with hypertension and the general clinic population, it is difficult to estimate the significance of this association.

It is possible that polycythemia vera belongs to a group of diseases including tumors of the brain and spinal cord, prostatic disease, chronic nephritis, chronic cholecystitis, and diseases of the thyroid gland, particularly toxic goiter, in which gastric and duodenal ulcer are apparently more commonly seen at necropsy than in other conditions.

Since there has been shown to be a direct relationship between secretion of certain constituents of the gastric juice and hematopoietic activity of the

bone marrow, there is much interest in the speculation that a disturbance in gastric function may be of importance in the development or continuance of polycythemia vera

Tuchfeld¹¹ and Morris¹² have suggested the hypothesis that production of an excessive amount of hematopoietic factor may be responsible for increased formation of erythrocytes, and experience has shown that in some of these cases repeated loss of gastric juice by tube has resulted in a decrease in the erythrocyte count. Unfortunately, we do not know the exact relationship of the secretion by the stomach of acid and hematopoietic substances. It has been suggested that the secretion of one is independent of the other, and that in the absence of secretion of acid there may still be secretion of the blood-stimulating factor. On the other hand, we do not know that secretion of excessive amounts of acid also indicates that larger than normal amounts of the erythropoietic substance is also being secreted. If the latter is true, one could perhaps explain the apparently greater incidence of duodenal and gastric ulcer in polycythemia on the basis that the associated hyperacidity and hypersecretion in cases of ulcer indicated a greater secretion of erythropoietic substance and, therefore, more blood formation.

In the cases we have studied there has been little to support this hypothesis. There was no demonstrable evidence of secretion of large quantities of hydrochloric acid in the majority of our cases, and only moderate hyperchlorhydria in some of the cases with ulcer. On the other hand, the apparent occurrence of symptoms of ulcer antedating the onset of polycythemia in most of the cases studied by us might be considered supportive evidence. Subsequent studies should help in elucidating this problem.

We have no definite information regarding the relationship of thrombosis of the vessels of the duodenum to the development of duodenal ulcer among patients with polycythemia vera. There seems to be some merit in the hypothesis in view of the known tendency of polycythemic blood to form thrombi and the suggested relationship of vascular changes in the duodenum and stomach to the formation of peptic ulcer.

SUMMARY

In 8 per cent of 142 cases of definite polycythemia vera there was roentgenologic or pathologic evidence of gastric or duodenal ulcer. In a control group of cases of hypertension and in the general clinic population the incidence of ulcer was 2.0 and 3.2 per cent, respectively.

It is pointed out that, with our present information, it is difficult to evaluate the significance of this association of diseases and that there is insufficient evidence to establish a distinct relationship between polycythemia vera and peptic ulcer.

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THE PRESENT STATUS OF THE PROBLEM OF "RHEUMATISM", REVIEW OF RECENT AMERICAN AND ENGLISH LITERATURE ON "RHEUMATISM" AND ARTHRITIS

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IN THREE PARTS

PART III†

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CHEMICAL AND ENDOCRINE ARTHRITIS

Under the term "chemical arthritides" can be conveniently grouped a number of joint diseases which are apparently closely related to chemical or metabolic alterations or to immunologic reactions. The forms of joint disease in which some chemical alteration (primary or secondary), or "chemical inflammation," seems to be the chief feature are gouty arthritis, arthritis of serum sickness, and hemophilic arthritis, to which list might be added intermittent hydrops, possibly an allergic arthritis from food, and ochronosis with alkaptonuria. Since the established endocrine disturbances are essentially chemical, a discussion of endocrine arthritis is included.

Endocrine Arthritis The literature contains such terms as chronic thyroidal rheumatism, arthritis thyreopriva, endocrine or hypoglandular arthritis, climacteric or menopausal arthritis, arthritis ovarioopriva, and polyarthritis acromegalia. Some are now attempting to launch "parathyroid

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arthritis" In any consideration of the endocrine glands and arthritis a definite distinction must be made as to whether the supposed endocrine disturbance is regarded as the sole or chief cause of the type of arthritis under discussion, or whether it is looked upon merely as a predisposing or aggravating factor of an arthritis primarily not endocrine Certain endocrine relationships have been noted in both atrophic and hypertrophic arthritis, occasional alterations in metabolic rate being the most concrete examples Almost every ductless gland has been suspected of being the cause of arthritis, but the thyroid and ovaries are suspected most often There are sharp divisions of opinion as to whether an entity such as climacteric arthritis or any other form of "endocrine arthritis" really exists³⁸⁸ Saxon³⁸⁹ and Jezierski (1931) favor the existence of such an entity Saxon cites the usual arguments frequent coincidence of menopause and hypertrophic arthritis, occasional lowered metabolic rate in both types, prevalence of arthritis where goiter is endemic, supposed benefits of endocrine therapy or pelvic diathermy, and so on He found a lowered metabolic rate in about 50 per cent of an unstated number of cases of chronic arthritis, but thyroid medication only helped those patients who were obese or had signs of hypothyroidism Ovarian therapy was not successful Jezierski urges the use of Abderhalden's method and the interferiometric test to uncover endocrine arthropathy, which he describes as painful creaking, without much exudation, in knees especially but in other joints also The use of oophorin tablets, follicular injections, or soluble ovarian extracts is recommended, and massage and radiotherapy are not indicated

Arthritis and Parathyroidism It has recently been suggested that patients with parathyroidism frequently demonstrate arthritis, that at least in certain cases of arthritis, especially "ankylosing spondylitis" or polyarthritis, there are signs of parathyroidism and that the arthritis may be due thereto, and that in such cases parathyroidectomy gives relief (Ssmarin (1928), Oppel (1929), Taddei (1929), Leriche and Jung (1930, 1931), Simon (1931), Simon and Jung (1931), Ballin and Morse (1931)) Others have denied such relationships The argument has been continued, with Funsten³⁹⁰ and Ballin³⁹¹ in favor of, and Bauer,³⁹² Compere³⁹³ and Nachlas³⁹⁴ against, the proposition

Among 95 patients with "arthritis, chiefly of the ankylosing type" Funsten noted 24 whose symptoms were suggestive of parathyroidism The values of serum calcium were intermittently elevated Parathyroidectomy was performed by Ballin in 14 of Funsten's cases All but one patient improved (9 markedly, 4 moderately) within 4 to 18 months

Bauer, Compere, and Nachlas protested, as did Welti (1931) and Lievre (1932), against the adulteration of the syndrome of parathyroidism with arthritis They conclude that there is no clinical, chemical, or pathologic evidence of any relationship No evidence of true arthritis was found in seven cases of proved parathyroidism seen by Bauer (in one case even after 13 years of parathyroidism), or in more than 50 proved cases reviewed by

Compere No negative calcium balance was found in any case of arthritis of either the hypertrophic or atrophic type. In provable parathyroidism, the serum calcium is permanently, not intermittently, elevated. In none of the cases of supposed parathyroid arthritis were full metabolism studies carried out, and in no instance was a definite adenoma found at operation. Such relief as was obtained by parathyroidectomy must have been nonspecific, as after almost any procedure involving anesthesia and rest. Johnson³⁹⁵ readily produced experimental parathyroidism and the picture of *osteitis fibrosa cystica* in animals, but arthritis was not evident. There is thus no justification for parathyroidectomy for arthritis and no proved connection between arthritis and parathyroidism.

Conclusions on "Endocrine Arthritis" While it is apparent that alterations in endocrine function may prepare the soil for, or may aggravate an existing, atrophic or hypertrophic arthritis, it is obvious that no convincing proof exists as to any primary endocrine arthritis. In acromegaly and in parathyroidism, the lesions are chiefly in bone. Secondary and relatively minor changes may become evident in joints, but "true arthritis" is not a feature. Neither atrophic nor hypertrophic arthritis is proved to be primarily endocrine in origin, nor is any other type of arthritis, for that matter, in the sense that the administration of a known endocrine product or the removal of a ductless gland is followed by unqualified improvement or cure comparable to the use of insulin in diabetes, removal of the thyroid in hyperthyroidism, or use of thyroid extract in myxedema. The closest that the disputants have come to agreeing on an "endocrine arthropathy" is in the cases of "villous arthritis," which others insist is not essentially an arthritis but a dry, proliferative, fibrous or villous synovitis. Even here, convincing clinical, pathologic, and therapeutic proof is almost entirely lacking. (To one of us [Hench], the most likely candidates for such a title would seem to be gout and hemophilic arthritis. Both are strikingly sex-linked. Metabolic or chemical alterations are their chief feature, and recent experience in medicine suggests that "metabolic" or chemical diseases are frequently being proved to be endocrine. Proof that gouty and hemophilic arthritis should be called endocrine awaits future studies—Ed.)

Gout and Gouty Arthritis Gout is a unique disease. Its ancestry can be traced back to the beginnings of recorded medicine. Its genealogy is most distinguished: no disease has a more noble pedigree or has enjoyed more regal patronage. Its drama unfolds with spectacular abruptness. Its violent torments may continue with a degree of pain which approaches the most agonizing in human experience, at times challenging all endurance. But in spite of these arresting attributes, gout, "the king of diseases and the disease of kings," faces the fate of its royal patrons—oblivion. It would seem that gout has almost disappeared from indexes of medical literature and been practically exiled from the reckonings of physicians. "Acute old-fashioned gout" has recently been commented on editorially as "an almost extinct disease."³⁹⁶ For the last 15 years there have appeared in all jour-

nals printed in English a yearly average of only two articles thereon (Hench and Darnall³⁹⁷) Gout has by no means disappeared, as the statistics of several critical observers reveal By them it is seen with increasing frequency, its proportionate incidence has been noted Not has present-day gout "gone modern" or changed its character in any important particular The gout of today presents the same clinical pattern, the same diagnostic criteria, the same characteristic "chain of fits" as in Sydenham's day It is, however, still very likely to be mistakenly diagnosed as either acute rheumatic fever or chronic infectious arthritis

Definition and Pathogenesis of Gout More than 40 years ago Osler, in his first edition (1892), defined gout as "a nutritional disorder associated with an excess formation of uric acid" Three current definitions are that gout is (1) "A disease characterized by abnormal metabolism of purines, whereby the uric content of the tissue fluids is eventually elevated, and at variable stages, usually late, salts of uric acid are deposited as tophi in particularly affected parts of the body" (Wilder³⁹⁸), (2) "A disturbance of purine metabolism characterized by an inflammation of joints, either acute or chronic, and attended in most cases by the deposition of sodium urates in or about the affected joints" (Pratt³⁹⁹), and (3) "A hereditary disease characterized by dysfunction of nuclear metabolism with an increased uric acid content in the body tissues" (Watson⁴⁰⁰) The chief progress discernible in these changing definitions is that Osler's idea of an excess formation of uric acid in gout has generally been discarded

The theory of excessive production of uric acid is untenable because an accumulation of uric acid has never been found to be associated with an increased excretion or accumulation of phosphates such as would be demanded by an accelerated destruction of nuclear protein (Wilder) However, the possibility that there may exist some source of uric acid other than nucleoprotein has not been excluded Uric acid in birds and reptiles is mainly derived by synthesis in the liver of urea and lactic acid Were some such synthesis possible in man, urates would accumulate without accompanying phosphates Wilder admits that such a synthesis in man is probably incapable of demonstration, but suggests the conception that certain persons with gout may possess some such primordial metabolism as a vestigial characteristic

Although the evidence indicating abnormal purine metabolism is associated with the most prominent features of gout, the present view is that such an abnormality may be the result rather than the cause of gout, and will prove to be a matter of secondary importance Knaggs¹⁹⁷ has suggested that urate deposition is relatively unimportant in the pathogenesis of gouty arthritis, that it is the minor effect of certain metabolic changes which, in addition to urates, produce simultaneously other bodies having toxic effects According to Knaggs, gout is closely akin to rheumatoid affections In the absence of deposits of urates it is impossible to distinguish the gouty joint from one that has the characteristics either of atrophic arthritis or of hyper-

trophic arthritis. Numerous joints with urate deposits show other arthritic changes which completely overshadow the ones that justify their inclusion in the gouty category. Arthritic changes in the gouty joint may be caused by (1) toxins resulting from a disordered purine metabolism, and (2) probably the equally or more important toxins that may be the same as those responsible for atrophic and hypertrophic arthritis. In the Strangeways collection nearly every specimen of gout presents hypertrophic bony phenomena which are apparently later followed by degenerative changes similar to those seen in atrophic arthritis. Inflammation set up by urates is responsible for introducing an element of confusion and intensifying the pathologic reaction. The characteristic pathologic changes in gout are illustrated in Knaggs' article by several excellent photomicrographs by Rodman. Watson has accepted the idea of Llewellyn (1927), Gudzent⁴⁰¹ and others, that the exciting cause of gout is cellular sensitization, in other words, an allergic response, exciting factors being endogenous or exogenous proteins of pathologic or biochemical origin, and the predisposing factor being "heredity." Alter⁴⁰² believes that gouty arthritis is at present the only definitely recognizable form of "metabolic arthritis."

Diagnosis of Gout The usual but not always correct conception of gout is revealed in Alter's⁴⁰² description of its characteristics. "Acute gout comes on suddenly with severe pain, usually in the great toe, and most often in the middle of the night. In chronic gout recognition of tophi makes the diagnosis certain. The blood in a gouty subject shows a constantly higher level of blood uric acid. The roentgen-ray appearance shows the so-called punched-out areas which are deposits of urate crystals." These remarks are only relatively true, for as Hench and Dainall,³⁹⁷ Wilder³⁹⁸ and Watson⁴⁰⁰ have all stated, a joint other than a great toe may be affected first, great toes may long escape involvement, and the diagnostic value of the determination of uric acid in the blood has often been disappointing, as normal concentrations of uric acid may be found in early, even in late, cases of proved gout. Tophi often do not appear until years after the initial attack, punched-out areas in bone appear also in atrophic arthritis and, when they appear in gout, they often do so too late to be very helpful.

An insistence on the "classical picture" ("toe and tophus") before a diagnosis of gout is made, is responsible for its nonrecognition in many provable (tophaceous) cases, and in many other cases of definite but early (pre-tophaceous) gout. Citing Hench's experience, Wilder emphasizes that the diagnosis of gout must depend to a large extent on a history of previous acute and generally short attacks of arthritis with complete remissions in early attacks. According to Hench and Dainall, an attack of acute arthritis in one or more joints, coming a few days after a gastronomic celebration or shortly after an operation, should be looked on as possibly gouty in nature. Patients have presented themselves in attacks of undoubted gout precipitated by the Feast of the Passover. Although surgery has been noted occasionally as one of the determinants of gout, surgical operations have not yet received

sufficient recognition as excitants of the disease. The experience of Hench and Darnall has led to the useful axiomatic generalization to "suspect gout in cases of acute postoperative arthritis." Since the advent of liver therapy for pernicious anemia, the occasional occurrence of gout during such treatment has been reported. Sears ¹⁰³ reports another such instance, acute gout appearing on the thirty-sixth day of liver administration.

By those of widest experience, "irregular gout" has become a subject approached gingerly and considered with little sympathy. Schmidt ⁴⁰⁴ has reported the case of a patient with supposed gout who experienced a number of "abortive attacks" characterized by redness and swelling of the skin of an extremity without any joint symptoms. "The attack of gout ran its course, as it were, externally in the skin." (The chemistry of the blood and urine before and during an "attack" was apparently characteristic of gout. However, no tophi were present, and the fall of blood uric acid from a single value of 9.6 mg. before an attack to 1.9 mg. is a drop of unusual magnitude, of such a degree as to be viewed skeptically.—Ed.)

Roentgenograms. Roentgenographic findings in various stages of gouty arthritis have again been briefly summarized by Scott ³²⁴. Characteristic alterations are best seen in roentgenograms of hands (or feet—Ed.). When gout attacks a major joint, there are no roentgenographic changes of diagnostic value. Coincident roentgenograms of a hand (or foot) may be valuable, for small urate deposits are detected therein in nearly all cases of gout. Various stages of the disease, as illustrated in roentgenograms of the extremities, are, according to Scott, as follows. Very early cases show no articular changes, other changes are a single punched-out area at the base or head of bones making up a minor joint, occasionally a group of small transparent spots, frequently in the base of the first metacarpal, or involvement of the bones and joints of wrists producing characteristic carpal "mottling." Later, disorganization of joints occurs, with a loss of cartilage in joints showing gouty deposits. Irregularity and erosion of articular bone follows, and, finally, subluxation with almost complete destruction of articular bone. (In the experience of the editors, the earliest and most characteristic changes are seen in the feet more often than in the hands.—Ed.)

Treatment of Gout. While the treatment of gout is in general symptomatically satisfactory, it is not specific in any regard. The classic treatment of gout by restriction of purine, hot or cold applications, rest, and by preparations of colchicum and cinchophen, continues unchallenged. It has remained practically unchanged for years. When one recalls that aside from the use of cinchophen, introduced in 1908, there has been no major change in the treatment of gout since the introduction of colchicum in the sixteenth century, the appellation "Gout: the reproach of medicine" seems appropriate ⁴⁰⁵. Modern investigations have in part explained the rationale but have not materially altered the ancient principles of diet in gout. Favoring the allergic theory, Gudzent and Watson search for some type of food to which their patients with gout may be particularly sensitive. One such pa-

tient was thought to be sensitive to milk and fish "Avoidance of these quickly rid him of gouty symptoms and imparted a general feeling of well-being" Cuti-reaction tests are advised by Watson with appropriate desensitization by means of "specific antigens" "Should a gouty patient react positively to most of the cuti-reaction tests, a graduated course of peptone (Witte), 7.5 per cent, continued for two months or more will often desensitize the patient and incidentally (*sic*) relieve the gouty condition Instead of peptone, a mixed gonococcus vaccine frequently gives remarkably good results both in gouty conditions and true rheumatoid arthritis" (The theory of specific sensitization and desensitization seems out of place if gonococcal vaccine relieves or prevents gout—Ed)

Cinchophen The injudicious use of cinchophen over long periods may occasionally be responsible for a hepatitis, which may be fatal (Beaver ⁴⁰⁶), or from which the patient may recover (Weir ⁴⁰⁷ and Comfort ⁴⁰⁸) Many advise against the use of cinchophen, even in gout, on the ground that it is too risky Watson feels that "iodine in the form of potassium iodide, controls the gouty state quite as efficiently and much more safely" Considering the arguments for and against cinchophen, Hench ⁴⁰⁹ concluded that if other analgesics are effective, cinchophen products should be avoided When the former are ineffective, use of the latter is indicated Statistical data would lead to the conclusion that the chances of a fatal poisoning by cinchophen in a given case are in reality very slight (It has been estimated by the research department of one reputable manufacturing concern as about 1 in 600,000) Inasmuch as we use other therapeutic agents, which have at times toxic and even fatal effects, the use of cinchophen may be justified in spite of its occasional toxicity, particularly in frequently recurring and otherwise uncontrolled gout However, the physician and the relatives of the victim of severe hepatitis will find little consolation in statistics on the relative infrequency of such intoxications The present yearly rate of about six reported deaths throughout the world will doubtless increase as the condition receives wider recognition Cinchophen is sold in so many preparations and under so many names that it is almost impossible for patients taking medicine for chronic pain, rheumatic or otherwise, to avoid it at one time or another It would seem well to keep in mind the names of the more widely advertised preparations containing cinchophen Hench lists 30 such, with the fatalities or toxic reactions ascribed to each (Synthalin was included in error—Ed)

Wilder recommends the use of neocinchophen or, if cinchophen is used, he favors Weintraud's advice regarding the use of alkalis to prevent possible depositions of urates in acid urine When evidence of intolerance to cinchophen appears in the form of hives, skin rashes, gastric upsets, or icterus, the use of the drug should be permanently discontinued Mother-sole ⁴¹⁰ has objected to current methods of treatment and has championed the views of Haig, "whose opinions it has long been the fashion to belittle Those who follow Haig's teachings need not run the risk of poisoning their

patients with colchicum or atophan." Points of importance are not so much the avoidance of purines and proteins, but their ingestion in proper proportions, and particular care in the use of foods, drinks, and drugs which, according to Mothersole, interfere with the normal regulation of the hydrogen-ion concentration of blood and tissues. Various forms of physical therapy are distinctly helpful in gout. Calthrop¹¹¹ favors moist compresses, paraffin packs, and other procedures rather than local radiant heat which may be irritating and which, if used, should be applied only long enough to cause a mild hyperemia.

Comparative Value of Salicylates and Cinchophen in Gout Sodium salicylate is known to increase the concentration of urinary urates, and many believe that it does so as effectively and in the same manner as cinchophen—through its action in the kidney whereby renal permeability for urates is augmented. Others believe that the increased concentration of urates in urine reflects an augmented excretion, due in part to an increased uric acid production or to a diminished destruction resulting from the inhibition of the uricolytic ferments. Conflicting data on the effectiveness and manner of action of salicylates in augmenting urate excretion have been reviewed previously (Hanzlik, 1927).

To avoid toxicity caused by cinchophen there has been an increasing tendency to use salicylates as a substitute. According to Denis (1915), 45 grains of salicylates have very little effect, and to produce significant increase in urinary urates it takes about 100 grains—an amount generally not well tolerated by patients, at least not for more than a very few days (Chase, Myers, and Kilham (1921), G. Graham (1920 and 1926)). It has been noted also that although salicylates increase the concentration of urinary uric acid as much or even more than cinchophen, instead of preventing attacks they often provoke them (Noorden (1906) and Lublin (1930)).

According to Schroeder,¹¹² sodium salicylate augments urate excretion in rabbits and dogs, but only when it is given intravenously, and then only slightly. He accepts the evidence that, in man, it produces an augmented excretion. However, in rabbits and rats it also produces an increase in allantoin. From this and other evidence he believes that salicylates augment nuclear metabolism somewhat, thereby increasing the formation of the uric acid, which is followed by the appearance of more urates in urine. Salicylates may perhaps also reduce uricolytic enzyme action. Although an augmented urinary excretion of urates follows the use of salicylates, this increase does not compensate for the increase in urate production or for the possible decrease in its destruction. Schroeder found that only cinchophen and neocinchophen have a marked influence in preventing uric acid deposition or retention in the kidneys of dogs, cats, rats, or rabbits. Sodium bicarbonate and sodium salicylate have a slight effect, the bicarbonate more than the salicylate. Hexamethylenetetramine and piperazine had no effect in normal rabbits and dogs.

The Uric Acid Problem, Methods Because the determination of blood

uric acid is such an important aid in the diagnosis of gout, the method used must be highly reliable and must not give abnormal values that cannot be explained by the clinical presence of gout or some other disease occasionally associated with hyperuricemia. Jordan and Gaston⁴¹³ found consistently high values for blood uric acid with Koch's modification of Folin and Benedict methods, using the Folin-Wu filtrate. The new method of Folin, using unclaked blood filtrate, gave considerably lower values generally in keeping with the diseases studied. They considered four mg the usual upper limit of normal. (Osterberg⁴¹¹ also believes that the Koch modification gives results which are too high. In a series of 35 cases he further determined the blood uric acid values by the Folin method on "claked blood" and by the newer Folin method on unclaked blood. The older method gave consistently higher results, the difference averaging 0.5 to 1.5 mg per 100 c.c. of blood.—Ed.)

Physiology Three factors must be considered in studying the concentration of urates in the human body: the amount of uric acid formed from food (exogenous) and in the process of human catabolism (endogenous), that destroyed in the body, possibly by the liver and intestines, and the amount that remains and is excreted by the kidneys. When the level of uric acid rises in blood it does not necessarily mean that more urates are being retained and less excreted; it may represent an increased urate formation or decreased destruction. When the former occurs there should be appropriate increase in urinary phosphates as well as urates. Some have suggested that a sudden rise of the blood uric acid may represent "tissue liberation"—urates suddenly liberated from tissue depots—and that the excess of urates does not represent retention, as is the general implication, but that the urates are on the way out of the body, traveling from tissues into blood and not vice versa. Thus the probable direction of a hyperuricemic flow must be considered. When the level of blood uric acid falls, it may not signify an increased excretion but a decreased formation or increased destruction. Studies on physiology concerning urates and on the pharmacologic action of various substances and medicines presumably affecting the urates must take these points into account. Thus studies on "the uric acid problem" are difficult, as one must determine not only the concentration of blood but also that of urine, and when possible, of tissues. In addition, correlated studies on sulphates, phosphates, and, in animals, on allantoin are necessary to approach an adequate explanation of the processes under observation. The problem is made more difficult because the physiology of animals is not the same as that of man, and that of the patient with gout is again obviously, at least in some regards, quite different from that of the normal man or normal animal.

Studies on metabolism of uric acid in various animals do not reveal information directly applicable to human physiology, as metabolism of uric acid is not similar in different vertebrates. However, they do yield important data. Birds and reptiles excrete large amounts of uric acid in the

urine, as before stated, uric acid in them is formed mainly by synthesis of urea and lactic acid in the liver, a minor part arising from nuclear metabolism independent of the liver. Most mammals do not form uric acid from urea but only from products of nuclear metabolism. By a series of enzymatic reactions, uric acid is formed from nuclear protein, and almost all of it is excreted as such. In dogs (except the Dalmatian), uric acid is excreted normally only in traces, as it is almost entirely oxidized by liver enzymes and excreted as allantoin. Removing the liver, Bollman and Mann^{415, 416} show that this destruction or conversion of uric acid is completely prevented, urinary allantoin progressively decreasing and large amounts of uric acid appearing in blood to be excreted as such in urine. Injection of uric acid into a liverless animal was followed by its almost quantitative recovery in urine unchanged. Bollman and Mann conclude, therefore, that in dogs, the formation of uric acid is independent of the liver, but the destruction of uric acid (and formation of allantoin) depends entirely on the liver.

It is believed that in man uric acid is eliminated by glomeruli and reabsorbed by cells in the loops of Henle. Renal tissue has a peculiar affinity for urates. It retains injected urates in large amounts, and in animals at least, these urates which are stored in the kidney are not promptly excreted in urine but are first returned to the blood (Folin, 1924). It is believed by some that gout represents a state of abnormal renal tropism or affinity for urates resulting in a diminution of excretion. Medicines that are effective in gout are thought to act by altering this affinity of kidneys for urates, or by increasing urate excretion, possibly by diminishing the extent that it is reabsorbed in the loops of Henle.

In man, the fate of injected urates is not clearly understood. Large amounts are unrecovered, and apparently destroyed. In dogs, since most of the uric acid of either endogenous or exogenous origin is oxidized to allantoin, Wilhelmj and Moskowitz⁴¹⁷ have proposed the study of uric acid tolerance curves, the rate of disappearance of injected urates being an index of urate destruction. Following a single intravenous injection of uric acid, the blood uric acid rose to a high level and then began to drop. By replotting the curves, with the logarithm of the blood uric acid concentration against the time after injection, they found that the rate of disappearance was about 3 per cent per minute and that it followed a logarithmic curve suggesting a monomolecular reaction in which one molecule of uric acid is oxidized to one molecule of allantoin. The uric acid excreted in urine was small in amount, varying between 2.7 and 5.5 per cent of that injected. The continued injection of uric acid revealed that the ability of dogs to destroy uric acid is sharply limited. The effect of an added single injection during a continuous injection was also studied. Comparing these results with those in man, it was suggested that the difference between dog and man in this respect may be quantitative rather than qualitative.

The effect of the methylated xanthines, theophylline, theobromine, and caffeine, on the uric acid excretion of Dalmatian dogs was found by Hanzal

and Meyers ⁴¹⁸ to be essentially the same as that for man. There was no change in the quantity of uric acid excreted after administration of theobromine, but a marked increase after theophylline and caffeine. The solubility of several methylated uric acids was found to be much higher than uric acid. Those differences were made use of in a separation of the uric acid excreted after the ingestion of the methylated xanthines. Dreyer and Young ⁴¹⁹ studied the effect of various substances on the excretion of uric acid and urates by cockerels. They found that, of solvents for uric acid, the intravenous injection of lithium carbonate in isotonic concentrations is most effective, inducing marked diuresis and increasing the output of uric acid many fold. Lithium chloride, caffeine, theophylline, euphylline, colchicine, and epinephrine do so also, piperidine, piperazine, ethylene diamine, and hypertonic solutions of glucose, sodium sulphate, sodium chloride, and sodium bicarbonate increase the excretion less effectively. Methylamine, guanidine, and hexamethylenetetramine are ineffective. Theobromine and the salicylates are entirely negative.

Hemophilic Arthritis "Bleeder's Joints" The development of newer ideas on hemophilia has resulted in the appearance of several interesting reports on hemophilic arthritis (Rutherford,⁴²⁰ Freeman⁴²¹). Key⁴²² has given for the first time in English a detailed report on its pathology, and Keefer and Myers⁸³ describe clinical and roentgenologic features in five cases, with a review of the literature. According to Howell's theory, hemophilia is the result of a disturbance of blood platelets, which may be normal in number and morphologic appearance, but which fail to yield cephalin necessary for normal clotting processes. König (cited by Key) previously recognized three states of hemophilic arthritis: (1) simple acute hemarthrosis, with single repeated hemorrhages into joints, with pain and limitation of motion, (2) panarthritis, the form associated with an inflammatory process in joints, fever, hemarthrosis, and exudation into the joint, changes in synovial membrane, capsular thickening, with organization or exudate resulting in fibrosis, limitation of motion, swelling, and discoloration of joint surface, and (3) the chronic inflammatory stage, with chronic changes in joints and destruction of articular cartilages as in arthritis deformans. Key cannot differentiate the second and third types, and recognizes only two stages, that of acute hemarthrosis, and the stage of chronic arthritis.

Acute hemarthrosis usually follows some sort of an injury, but may occur spontaneously even while the patient sleeps. Pain and swelling may be slight or intense, varying with the degree of intra-articular pressure. Local heat and redness are generally not present, but periarticular tissues may appear cyanotic. Extrasynovial hemorrhages may appear as discolorations. There may be slight fever and moderate leukocytosis. In roentgenograms, bones may be normal in the acute stage but the joint is distended with blood, which casts a shadow denser than in ordinary acute synovitis. An irritative

hyperplasia of synovial membrane results from hemorrhage and pressure therefrom. Subsynovial tissues become thickened by fibrous tissue and contain large amounts of iron, in turn containing blood pigments which, according to Keefer and Myers, often cast a dense roentgenographic shadow and may be incorrectly interpreted as calcification. Macrophage cells accumulate in subsynovial tissue and migrate back and forth between the joint cavity and synovia, phagocytosing the erythrocytes, the pigment of which remains in the macrophage cells. When the blood is absorbed the tissues tend to return to normal. Each new hemorrhage adds irritation, and synovial villi form. After many hemorrhages, joints may fail to return to normal. Stiffness, swelling, and pain may ensue for weeks or months, progressing by remissions to the stage of chronic arthritis. Fibrous ankylosis may occur, bony union rarely results. The cartilage eventually erodes, at its margin, by encroachment of the hyperplastic synovial membrane, such as occurs in atrophic arthritis. A spotty destruction of articular cartilage occurs, the areas of destruction being irregular in contour, a characteristic of hemophilic arthritis. Cavity or cyst formation may result from subperiosteal hemorrhages or those in subchondral bone. Roentgenograms in the chronic stage present a variable picture, suggestive at times of tuberculosis, of chronic atrophic or hypertrophic arthritis, even of osteochondritis, and Key, Keefer, and Myers agree that they are not pathognomonic. The diagnosis of hemophilic arthritis rests chiefly on the history of a bleeding tendency and the onset of acute joint swelling after minor injury. The coagulation time is usually increased but may be normal. Aspiration of a joint for blood may at times be risked, using a very small bore needle.

Treatment of Hemophilic Arthritis Birch ⁴²³ has attempted to confirm Howell's theory and to show that, in men, hemophilia is apparently the result of a lack of ovarian hormone. As a result of her work, the idea of ovarian therapy, first suggested by Grant (1904) and Wright (1909) has been revived. White ⁴²⁴ prevented further hemarthrosis, in a boy, by repeatedly giving 0.5 c.c. of theelin, intramuscularly. When ovarian extract failed to control hemorrhages in two cases, Bernstein ⁴²⁵ gave 10 to 15 c.c. of whole blood, intramuscularly, every other day, taking the blood from the patient's mother, during her menstrual cycle, and continuing for a few days thereafter. (According to Matagne, 1932, Chaher considers frequent injections of mother's serum the most efficient treatment of all—Ed.) Kimm and Van Allen ⁴²⁶ injected 4 grains (0.26 gm.) of ovarian extract "azoule," an English preparation, to prevent further bleeding in a boy with hemophilic Volkmann's contractures. Spoto ⁴²⁷ considers the use of ovarian extract (Lilly No. 177) by hypodermic, and later by mouth, successful, but Freeman ⁴²¹ cited failures, and progynon failed to hasten clotting time in a case of Brown and Albright's ⁴²⁸. Key has outlined additional treatment for the joints in the acute stage, complete rest and immobilization in plaster or splint, in the chronic stage, correction of deformities by traction or wedging plasters, and if necessary, supports such as roller bandages and occasionally

a walking caliper Under no circumstances should the joint be manipulated or opened (Keefer and Myers ⁴²⁰)

Joint Conditions Associated with Purpura Schonlein's purpura (peliosis rheumatica) and Henoch's purpura (purpura nervosa) are associated with joint pains and swelling, and are classified by Otto ⁴³⁰ under the anaphylactoid variety of the primary type of non-thrombocytopenic purpura. In the former type epinephrine is used. The latter type, Henoch's, is thought to be due to the histamine-like action of split protein products absorbed into the body.

MISCELLANEOUS TYPES OF JOINT DISEASE

Intermittent Hydro-Arthrosis This is a rather rare disease, only 77 cases having been reported up to 1921 (Bierring). Affecting the sexes equally, it involves the knees most commonly. It is not possible to place it accurately in an etiologic classification as its cause is unknown. It is variously considered as a vasomotor neurosis related to angioneurotic edema, an endocrine disturbance, or an allergic reaction to bacteria or other agents. Distinction should be made between two so-called types, idiopathic and symptomatic. The first is presumably a painless intermittent "synovitis," or synovial effusion, occurring more frequently among young adult women. Some believe it to be related to menstrual irregularities. This type represents the rare true form of intermittent hydrops which, were it essentially a functional affair, would be expected to recur and remit more or less indefinitely yet produce little or no organic residue. Intervals of freedom generally vary from 7 to 21 days, usually being 11 to 12 days. The second or symptomatic type seems to be associated with arthritis and is less rare. Representing probably the early stage, it is perhaps the synovial element of a very slowly progressive arthritis, with complete remissions in symptoms but probably not in pathologic changes. Because of its rarity, a study of the pathologic findings in one case (apparently of the second type) by Porter and Lonegan ⁴³¹ is of special interest. When it was unrelieved by the usual treatments (desensitization with peptone injections, intravenous TAB vaccine, arsenic, quinine and its derivatives), synovectomy was performed on both knees. Pathologic changes in synovia resembled those found in atrophic arthritis: villous formation, thickening of synovial membrane, and mononuclear infiltration. The subsynovial layer, however, was markedly edematous, in some such areas the edema was replaced by fibrinous hyalinization, which with edema would be unusual in ordinary atrophic arthritis. Hydrops had recurred, with little variation, 9 years prior to operation, but had not returned five years after synovectomy. However, a progressive arthritis of hips and spine appeared.

Synovectomy was performed in two cases reported by Krida ⁴³². The swelling in the first case initially followed trauma, thus it may represent the symptomatic type. Skin tests to 137 substances, foods, and organisms were

negative Operation was done during the period of hydrops Blood counts and studies of the synovial fluid were normal Sections of synovial membrane showed flattened villi, new granulation tissue, edema, and profuse round cell infiltration The second case was related to menstruation and was apparently of the idiopathic type Synovectomy was done during the quiescent period, hence differences in pathologic findings were noted long slender villi, well formed connective tissue, only slight edema, and moderate round-cell infiltration Effusions had not recurred within one year and within eight months after operation, respectively

Krida has reviewed factors of age, sex, race heredity, and the possible etiologic connection with trauma, infection, arthritis, menstruation, pregnancy, psychic disturbances, and sensitization Under ordinary circumstances the prognosis for therapeutic or spontaneous cessation is not good, though both occur Good results were obtained from synovectomy by Bernstein in "several cases" of "recurrent hydrops"

"Mixed Types" of Joint Disease Certain patients present mixed types of arthritis and search may show an obvious combination of at least two causative influences or of two clinical types Coates⁴³³ describes combinations under the following headings atrophic arthritis and gout, atrophic arthritis and arthritis of the menopause, atrophic arthritis superimposed on hypertrophic arthritis, and gout and hypertrophic arthritis (Although patients with atrophic arthritis in later life often get hypertrophic arthritis, is not this to be expected, since the latter is almost universal after the age of 50? Cases illustrating the unmistakable combination of atrophic arthritis and gout are rare Coates' cases do not clarify the issue They seem poorly chosen to prove the point and clinical data are scant Thus of four patients with supposed gout only one had tophi and two without tophi were women Provable gout in women is very rare, and the statement that the "uric acid was high" and roentgenographic "cysts" were visible is not enough, without considerable more data, to convince critical readers that gout was present or that a mixed arthritis was in fact observed—Ed)

Arthropathia Psoriatica Psoriatic arthritis has been neglected in the English and American literature Psoriasis and arthritis may occur together casually and quite independently, but often in cases of long standing psoriasis a characteristic involvement of joints may occur which is favorably influenced by treatment of the skin condition (Garrod and Evans, 1924) Two cases of pustular psoriasis with arthritis are reported by Hunt⁴³⁴ Pain and stiffness in joints varied with the skin condition

Of 53 patients with psoriasis studied by Hunt,⁴³⁵ 70 per cent were suffering with "arthritis or rheumatism," 80 per cent had relatives with some form of rheumatic infection, and 35 per cent gave a familial history of psoriasis Because her patients complained of no one type of rheumatism but had, variously, atrophic or hypertrophic arthritis, rheumatic fever, or fibrositis, she does not recognize a specific type of psoriatic arthritis Because the histology of psoriasis has several points in common with that of

clinical or experimental rheumatic nodules, she suspects that the two diseases have a common cause, probably streptococcal (It is likely that Hunt saw cases of true psoriatic arthritis but did not recognize the entity and confused it with other types of rheumatism incidentally associated with psoriasis—Ed) Without mentioning arthritis Jamieson⁴³⁶ has reviewed the various theories on causation and treatment of psoriasis, outlined his favorite diet therefor, and considered the possible relationship of the disease to some endocrine abnormality, possibly of the pituitary gland

Arthritis and Leukemia A related arthritis is exceedingly rare in cases of leukemia although bone pains occur Four cases of arthritis associated with leukemia are reviewed by Smith⁴³⁷ Two new cases are reported one by Poynton and Lightwood⁴³⁸ and one by Smith, in both cases the preliminary diagnosis was acute rheumatic fever In the first, a girl, three years old, had fever and migratory joint pains, and later cough and a swollen tender ankle The liver and spleen were barely palpable The blood picture was that of an aleukemic phase of acute lymphatic leukemia (erythrocytes 1,125,000, leukocytes 4,700 per cubic millimeter, and lymphocytes 82 per cent) At necropsy, leukemic periosteal and medullary infiltrations were found Various cultures were negative In Smith's case a boy, three years old, was observed over a period of nine months in four acute exacerbations of acute polyarthritis that resembled rheumatic fever but were resistant to salicylates and other treatment Lymph nodes, liver, and spleen were enlarged The erythrocytes fell to 1,000,000 per cubic millimeter, the hemoglobin to 15 per cent The leukocyte count varied between 18,000 and 680 per cubic millimeter The diagnosis was leukopenic myeloid leukemia Roentgenograms revealed periosteal thickening, cortical erosion, and medullary rarefaction Death occurred in one year

"Hysterical Joints" The diagnosis and treatment of this condition are given by Ogilvie⁴³⁹ A dancer, 18 years old, fell and thereafter complained of pain in the hips and knees for which no relief was obtained by various treatments, including removal of the external cartilage from both knees Muscle spasm, great pain, and limitation of motion in hips and knees were present, but no atrophy of muscle, shortening, swelling, or abnormal reflexes were found (Roentgenograms were not mentioned) Significant pain in joints is almost invariably accompanied by wasting of related muscles "If there is no wasting the pain is either slight or imaginary" According to Ogilvie, disease of both hips and knees without involvement of upper extremities is almost unknown, occurring neither in tuberculosis nor in gonorrheal or atrophic arthritis Psychotherapy was successful

Periarthritis of the Shoulder Such a term seems preferable to Dickson,^{440, 441} and Dickson and Crosby⁴⁴² to "painful shoulder," "subdeltoid bursitis," or "subacromial bursitis," for the entity which it signifies results from a complex pathologic state in which not just a bursa is involved but also capsule, ligaments, and tendons at the shoulder Characteristics of the syndrome are the onset of pain, with or without trauma, the pain is

aching, or sharp and stabbing, sometimes severe enough to require morphine. Pain is felt a few inches above the insertion of the deltoid and may continue as a neuralgia down the arm. Sensation and reflexes are normal. The characteristic limitations are pain beyond abduction of about 45° and on attempting full external or internal rotation. Forward and backward motions are not limited and are painless. Sometimes abduction is only painful between 70 and 90° , beyond that angle it may be painless. Atrophy of muscle may appear. Calcification may be present in the supraspinatus muscle.

From a study of 200 cases Dickson and Crosby concluded that some general physiologic disturbance was responsible and that an exact evaluation of the importance of any one factor (trauma, infection, metabolic derangement) was impossible. Regardless of probable cause and whether treatment was removal of foci, physiotherapy, manipulation, or surgery, the time required for duration of the disease was remarkably constant, from one to six months. Cases were equally divided between the sexes, in most the condition occurred after 40 years of age and oftener in the right shoulder. In 13 cases both shoulders were involved. Trauma was reported in 34 per cent of cases, infected foci in 88 per cent, and metabolic disturbances (diabetes, hyperthyroidism or hypothyroidism) in 16 per cent. Thus in the majority of cases more than one possible cause was noted. Calcification was seen in 37 per cent and did not bear any relation to the severity, duration, or possible cause of the condition. It is no invitation to operation and tends to disappear under conservative treatment. Removal of the calcified area in five cases did not hasten recovery.

Treatment consisted of removal of infected foci, regulation of metabolism, a high vitamin-low carbohydrate diet, heliotherapy, and, in the acute stage, immobilization of the arm in moderate abduction and external rotation by means of traction. On the third day, diathermy and passive motion were instituted. Ninety-four per cent of patients recovered completely in one to six months. In 13 cases polyarthritis developed elsewhere in the body.

In many cases of bursitis at the shoulder, pain is relieved by downward traction of the arm, according to Ferguson⁴⁴³ who has devised a simple apparatus therefor. Radiotherapy relieved Kahlmeter's²² patients. "Cross-fire diathermy" and gentle exercises are approved by Kovacs⁴⁴⁴ for subdeltoid bursitis, he places reliance on Dawbarn's sign (when the arm hangs by the side, palpation over the bursa causes pain which disappears when the arm is abducted). The sign is valueless according to Hitzrot,⁴⁴⁵ who favors rest, sedatives, and hot moist applications in the acute stage rather than dry heat, diathermy, and massage. As the acute condition subsides, gradual abduction is indicated. Operation is generally only indicated in acute traumatic bursitis to remove blood and exudate from the bursa and to repair tears of the supraspinatus tendon. Cave,⁴⁴⁶ Beei,⁴⁴⁷ and Gordon⁴⁴⁸ all felt that deposits of calcium were no indication for operation, that they frequently resorb, and that while it is easy to operate it is not easy to find

the calcification If anything goes wrong, the surgeon leaves as much damaged tissue as he approaches Surgical removal of calcified deposits is only indicated, Hitzel feels, when they do not disappear and are associated with recurring attacks and residual disability (Aspiration or surgical rupture of certain bursae is at times as beneficial as resection—Ed)

DISEASES OF MUSCLES AND FIBROUS TISSUE

Muscular Rheumatism, Myositis, and Fibrositis Ignorance and confusion attend clinical and etiologic segregations of diseases of muscles even more than of joints They are considered under two groups the commoner ones, myalgia, "growing pains," fibrositis or myofibrositis, and infectious myositis, and the less common ones—myositis ossificans progressiva, progressive myositis fibrosa, and dermatomyositis

Myalgia and "Growing Pains" The myth that normal physiologic growth may cause muscle pains has been exploded Transient muscle pains of short duration are believed generally to be due to unappreciated sprains, minor injury, or passing infections Chronic muscle pains may be due to chronic fatigue of normal muscles, fatigue of muscles affected by orthopedic abnormalities (flat feet, scoliosis), and infections or toxins In many cases of myalgia no pathologic basis is discovered Some suggest that the pains result from bacterial toxins, toxins of fatigue, an irritation of nerve endings, or to the actual lodgement of germs in capillaries and tissue spaces At any rate, myalgia is but a symptom of several disease conditions, not an incident of normal growth It may eventually be possible to classify disease of muscle etiologically traumatic, infectious, chemical, neurogenic, to date, however, only clinical patterns can be given

Fibrositis It has been shown that what is generally called "muscular rheumatism" is in reality not a myositis in the sense that primary parenchymatous changes in muscle cells are visible Indeed, true myositis, in the latter sense, is rare Common "myositis," or "muscular rheumatism," has been more properly designated as "fibrositis" by Gowers (1904), Stockman (1904 and 1920) and others, since its pathologic characteristics are interstitial not parenchymatous, an inflammatory hyperplasia of supporting fibrous tissue Inasmuch as the reaction may affect fibrous tissue, not only of muscles but anywhere in the body, the symptoms and anatomic types of fibrositis are varied as fibrous tissue of fascia, aponeurosis, tendons, capsule, and periosteum are involved Thus bursitis is sometimes spoken of as bursal fibrositis, a sciatic neuralgia as fibrositis of the coat of the sciatic nerve Fibrositis may be local (in a bursa, nerve, ganglion, one tendon attachment, or one muscle group), or generalized Thus various writers include under fibrositis such manifestations as lumbago, wry neck, tennis elbow, tender heels, Dupuytren's contracture, diffuse muscular fibrositis or "neuromuscular pains," tendinitis, "capsular rheumatism," and also sciatic or brachial fibrositis (Willcox, Brown,²⁹⁰ Buckley⁴⁴⁹)

The general and sex incidence of fibrositis has been noted (ANN INT MED, 1935, viii, 1321) It may constitute from 15 to 62 per cent of cases in various series on "rheumatism" It is more common among men than women (Coates and Delicati²³), and among miners and outdoor workers (Buckley,⁴⁴⁹ Holt²¹) than others With atrophic and hypertrophic arthritis, it makes up the three great types of chronic rheumatism

Its pathologic characteristics are reported (Stockman (1920), Brown²⁹⁰) as diffuse and localized inflammatory hyperplasia of fibrous tissue The localized areas may be palpable as nodules, tender areas of infiltration in muscles or near tendon attachments The nodules consist of a core of granular debris, presumably disintegrating small, round cell infiltrations, surrounded by concentric fibroblasts By special staining Stockman showed occasional nerve fibrils embedded in nodules, hence their painful character English writers stress particularly the diagnostic importance and apparent ease of finding nodules Some insist on their presence for a diagnosis, others admit that in many cases of fibrositis no nodules are felt Even when nodules are felt they may not reveal pathologic change, according to Nicola³⁸² who describes "myogeloses" as definite, sharply-localized areas of hardening 0.25 to 4 cm long, in muscles, chiefly gluteal They may be the cause of low back pain and are distinguished from the indurations of myositis in that biopsy is negative According to him they are due to localized interference with circulation and to local increase of lactic acid

Etiology of Fibrositis Some consider all forms of fibrositis of infectious origin, others believe one can have traumatic and other forms of fibrositis (gouty, toxic, and so forth) The chemical and pathologic differences between localized acute fibrositis (e.g. lumbago), chronic diffuse fibrositis (diffuse muscular rheumatism), and the fibrositis which is part of rheumatic fever are not established Brown looks on the reaction as a defensive one—an attempt to shut off the activity of the invading agent Willcox¹⁹⁸ believes streptococci responsible Seham and Hilbert⁴⁵⁰ consider certain proposals that the muscle pain is the result of colloidal changes, a general hyperalgesia, or of fatigue toxins accumulated as the result of circulatory disturbances and oxygen deficit in muscle Cold and damp are predisposing factors (Buckley⁴⁴⁹)

The "muscular rheumatism" of children was studied by Seham and Hilbert 21 per cent of 208 children from 8 to 15 years of age had muscle pains of from three months' to three years' duration Statistics of others vary between 7 and 44 per cent There were relationships between muscle pains, inadequate sleep, and fatigue Some had had occasional fever, but no more than a normal group would have had Of those with continuous fever 30 per cent developed systolic murmurs as compared to their appearance in only 19 per cent of those who were afebrile Nodules were not found The presence, absence, or removal of tonsils seemed to play no rôle The average agglutinative titer of serums for the normal group was 1:160, for those with muscle pains, 1:1,500 It was concluded that infection was

probably the cause of such muscle pains, at least some of which were related to rheumatic fever. Pains of chronic fatigue affect chiefly muscles of the lower extremities, are not migratory, not associated with joint pains, not affected by seasons of the year, are absent during sleep, and are cured by "adequate health schedules."

Common sites for fibrositis are muscles of the scalp and back of the neck, erector spinae, muscles of the loins and buttocks, and those of the shoulder, intercostal, or pectoral regions. Pain frequently is projected down the arms (Buckley).

Treatment of Fibrositis The treatment of muscular fibrositis is essentially similar to that of other forms of rheumatism: rest and heat, removal of foci, proper clothing and climate, analgesics, and sometimes vaccines. Buckley approves of the use of a hot flatiron applied to the back over a layer of thick brown paper when less primitive measures are not readily available. Sunshine is more useful in fibrositis than in arthritis. Roentgenotherapy relieved 65 per cent of 34 patients with lumbago who were treated by Kahlmeter.²²

Tendinitis Tendinitis may appear as part of atrophic arthritis, gout, or rheumatic fever, but it is often an independent entity. Kahlmeter⁴⁵¹ has discussed the various forms of localized and general tendinitis. Subdeltoid or other calcareous bursitis may in fact be localized tendinitis, other examples of which may be seen at tendon insertions of the great trochanter, the inside aspect of the knee, and the calcaneal spur. "A little known but not uncommon form" is that at the insertion of the quadriceps tendon at the upper border of the patella. Roentgen therapy is his favorite treatment, heat and massage being "rarely of any use." Kahlmeter considers trauma the most likely cause of quadriceps tendinitis.

Dupuytren's Contraction An extensive review of this disease is given by Davis and Finesilver.⁴⁵² Some consider it fibrositis of the palmar aponeurosis. It is a "focal hypertrophy of the connective tissue originating in the wall of the smallest vessels and ending in contraction." The usual etiologic factors, of heredity, trauma, infection, and endocrine deficiency, have been proposed and are discussed by these authors, who conclude from a study of 40 cases that the cause is unknown. Mild trauma may act as an inciting or contributing factor, it is not the specific cause, nor is there any known constitutional disease with which it is exclusively associated or of which it is a manifestation. The clinical course begins insidiously, with the formation of a small nodule or slight induration of the skin on the palmar surface of the hand, at the base of the fourth or fifth fingers, and slowly progresses in characteristic fashion. When the process has existed for some time, tendons become shortened and joint surfaces are changed in form on account of the change in pressure, becoming atrophic where the greatest pressure occurs. Joints may finally ankylose. It was more common among men (35 cases) than women (five cases) and among diabetics than non-diabetics (six of 200 diabetics had it). Medical measures seemed to be of

no avail once it had progressed. Excision of palmar fascia and digital fasciculi are advised. For reasons stated, the authors propose in the future to try division of the palmaris longus tendon in the wrist, in early cases.

Myositis Ossificans Progressiva This is a rare disease of the locomotor system which occurs among children during the period of growth and affects not only muscles but tendons, ligaments, fascia, and aponeurosis. It is characterized by the appearance of areas of calcification. There is no ossification of muscle, as muscle cannot turn into bone. There is ossification of fascia, and the formation of new bone is intermuscular, not intramuscular. Thus Grieg's term, "fibrositis ossificans progressiva," is more accurate. The condition proceeds by a series of acute exacerbations and remissions. Mair⁴⁵³ has reviewed the features in the 72 cases in the literature and added two cases of his own. An extensive review of ideas on cause, pathology, and treatment is included, but the former is admittedly unknown and no treatment seems helpful. It must be distinguished from myositis fibrosa, dermatomyositis, polymyositis hemorrhagica, and calcinosis interstitialis. A case of myositis ossificans is added by Jamieson⁴⁵⁴.

Generalized Myositis Fibrosa This is the rarest of all generalized chronic myopathies, there being only 4 authentic typical cases reported, according to Schwab, Brindley, Bodansky, and Harris⁴⁵⁵ who add a case of their own. Its characteristics are briefly insidious onset of stiffness and muscular clumsiness, weakness, loss of weight, progressive muscular disability, a doughy feel to muscles at first, later a sense of board-like hardness. Pain is not a striking feature. Biopsy of muscle shows degeneration, inflammation, and fibrous tissue changes, the disease being chiefly parenchymatous. Studies on creatine metabolism showed a definite relation between the degree of inflammation and the amount of creatine which the muscle contains and which it is capable of storing. Marked creatinuria and an extremely low tolerance for exogenous creatine were features of perhaps diagnostic importance. The cause is unknown. The prognosis is poor—death usually occurs in a few years. Specific treatment is unknown.

SCIATICA

Sciatica, or sciatic pain, is generally divided into two groups: (1) primary or idiopathic sciatica, in which pain is apparently the result of pathologic processes involving the nerve itself, producing "sciatic neuritis" and (2) secondary or "symptomatic sciatica," or "sciatic neuralgia," in which the pain is the result of factors which affect bones and muscles primarily and involve the nerve secondarily. Several (Gardner,⁴⁵⁶ Williams,⁴⁵⁷ Pringle,⁴⁵⁸ and Craig and Ghormley⁴⁵⁹) have reviewed these types, and the causes and treatment of the sciatic syndrome. Gardner classifies sciatica as follows: (1) the sciatic syndrome secondary to general disease, such as syphilis, diabetes, lead poisoning, and alcoholism, to tumors, or to "true inflammations" of vertebrae, pelvic bones or pelvic organs (in such cases pain is often bilateral and wasting of muscle or paralysis and disturbances in

sphincters may be present), (2) true sciatic neuritis, a rare disease, caused by exposure and infection, (3) sciatica due to myositis or fibromyositis, and (4) sciatica due to neurodocitis—an inflammatory condition of the intervertebral bony canal through which the nerve passes. From 80 to 85 per cent of the cases belong to the last two types.

Of 85 cases of sciatic pain studied roentgenographically by Williams, 80 (94 per cent) showed pathologic changes in tissues or joints, considered to be the cause of the nerve irritation. A narrowed lumbosacral disk was found in 59 cases, hypertrophic arthritis in 15, sacro-iliac arthritis in three, spondylolisthesis in two, and lumbosacral anomaly in one.

Among patients with sciatica there is frequently a contralateral scoliosis, a spinal tilt away from the affected side. Less commonly the trunk may list to the affected side, homolateral scoliosis. Capener⁴⁶⁰ saw three cases in which the scoliosis alternated from the contralateral to the homolateral side and back again. An instance of sciatica with paralysis following forceps delivery was encountered by Bugess⁴⁶¹, recovery followed rest, splinting, and massage. By simply increasing the heel-length of the right shoe, Hench, Wakefield, and Camp⁴⁶² promptly cured a patient with persistent sciatica resistant to all usual measures, and found to be associated with, and apparently due to, postural trauma incident to congenital hemi-hypertrophy and shortening of the left leg.

Treatment of Sciatica Ultimate success in treatment obviously depends on determining the likely one of the many causes noted. In general, rest in bed, heat, and analgesic drugs are indicated. Epidural injection is advised if these do not suffice (Gardner). Later detailed investigation must follow the acute phase. Treatment varies with the findings. Immobilization by strapping with adhesive plaster or casts may be necessary (Gardner, Williams). When significant symptoms recur, in appropriate cases Williams favors lumbosacral fusion. The results of various treatments and combinations of treatments of 159 cases of sciatic pain of indeterminate origin were analyzed by Craig and Ghormley, of these, 177 patients were ambulatory, 42 bedfast. In the former group of 80 treated with epidural injections alone, only 52 per cent were completely relieved. Obviously, other measures are indicated. Diathermy alone completely relieved 33 per cent of 36 patients, a belt and diathermy completely relieved 33 per cent of 52 patients. Injections and diathermy helped more, but the best combination was the use of epidural injections, diathermy, and a belt, by means of which 85 per cent of the group so treated were completely relieved. Of those confined to bed, 86 per cent of 28 patients were completely relieved by the use of a double Buck's extension, diathermy, epidural injections, intravenous foreign protein, and removal of foci. Of 14 patients treated similarly except that epidural injections were omitted, 63 per cent were completely relieved. Thus epidural injections gave added relief. They are also approved by Fulcher,⁴⁶³ Fletcher,²⁵⁶ L. F. Miller,⁴⁶⁴ and Bankart.³⁷⁷ Forty to sixty cubic centimeters of a one per cent solution of procaine hydrochloride seem favored.

Physiology of Joints The last should be first. A full understanding of the pathogenesis and treatment of diseased joints must be based on a comprehensive knowledge of the physiology of normal joints. Information on this subject is meager, and only a few workers seem to be putting first things first, going back to essentials. Much time is spent on a search for bacteria, on analyses of blood, urine, feces, and so on, but only a few bold spirits dare to violate the integrity of the joint cavity to study the cytology and chemistry of articular tissues in health and disease. Colloids and other substances are hopefully administered by vein, without our knowing whether the particular colloid will ever arrive at joints in significant amounts. So little is known of the blood and nerve supply of joints, of the origin of synovial fluid, of its physiologic reaction to different agents. Vaubel⁴⁶ studied the growth of synovial tissues of rabbits. There developed polymorphic cells clearly different from fibroblasts. These synovial cells are peculiar in producing mucin and a proteolytic ferment, and in forming in their cytoplasm large, highly-refractive granules. They can coagulate plasma under certain conditions. A function of these cells is to produce mucin for synovial fluid. Vaubel concluded that synovial fluid is a persistently liquid, ground substance derived from these special synovial cells which he calls "synovioblasts." Speculating on the etiology of atrophic arthritis, Bauer, Bennett and Short²²⁰ ask whether it is possible to produce the proliferative changes of this disease by simply interfering with or altering the physiology of a normal joint. From experiments they conclude that synovial fluid is probably a simple diffusate from rich subsynovial blood vessels, that proteins can be removed from joints only by way of lymphatics, and that albumin can leave joints with comparative ease, globulin with great difficulty. The size of a molecule that can be removed from a joint with ease lies, therefore, somewhere between a molecular weight of 72,000 and 175,000. If proteins are not removed from joints as rapidly as they gain entrance, an effusion results and is maintained. Thus a joint effusion may result from too rapid diffusion of plasma filtrate from subsynovial blood vessels into the joint cavity, from interference with the removal of proteins, or from a combination of these two factors. An increased permeability of vessels from any cause may result in a more rapid formation of synovial fluid, much richer in protein than normal. This increased protein attracts more water because its presence greatly increases osmotic pressure. Given a joint effusion, we have an ideal culture medium for connective tissue growth because it has a high protein content and contains fibrin and constituents of serum. The continued presence of fibrin is probably followed here, as elsewhere, by proliferation of fibroblasts, and vascular endothelium.

The importance of studies of this fundamental type is being increasingly recognized. Far-seeing clinicians are urging more studies of the patient's soil, less perhaps of the seeds of disease, for if the soil is not receptive the seeds fall by the wayside, harmless saprophytes. The determination of what agents *can* produce disease in joints may help to show what *does* produce a

given type in man, but while studies continue on likely agents, inquiry should be pressed regarding the sociology and chemistry of those recognized as physiologic candidates for the disease as well as of established hosts. Major secrets concerning arthritis await him who will but study the soil, especially the chemistry, of articular tissues in health and disease.

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EDITORIAL

ON WORMS

THE influence of intestinal parasites upon the health of the host has been a matter of lively discussion both in medical and lay circles through the ages. There have been periods when it was customary to attribute almost every possible malady to some harmless or even to some totally imaginary helminth parasite. Contrariwise in some ages medical opinion has favored the view that such parasites were not only harmless but indeed helpful, stimulating the digestion as some thought by consuming the excess of chyme. Even today there are native peoples such as the Abyssinians who are dissatisfied with the condition of their health if their stools do not contain segments of taenia. Those who are presumably better informed will perhaps question this criterion of well being, a wider knowledge of the variety of worms in the animal kingdom will enable them to discuss these under the headings of the platyhelminthes or flat worms and the nemathelminths or round worms and to point out that either in the larval or adult stage one or another of these helminths may parasitize nearly every organ and tissue in the human body. Even in the cases of those worms which in the parasitic stage remain confined to the intestinal tracts of their hosts there are some concerning whose pathogenicity very little doubt exists. The very name given to our common hookworm *Necator americanus* (American murderer) is an indictment, and the relationship of *Diphyllobothrium latum* to a severe macrocytic anemia is widely accepted. If, however, someone with a leaning towards the Abyssinian point of view were to question one of the well informed still more closely, especially as to the nature of this pathogenic action of the intestinal helminths, it would not be difficult to disclose a quite surprising state of ignorance.

Surprising, because after all physicians have been acquainted with worms in the intestine since long before Hippocrates. The Egyptians fifteen hundred years ago knew ascaris and oxyuris and taenia. Hippocrates himself held to a theory that worms were formed in the fetus and hence were present at birth. Later the mode of origin of worms became the test case in the endless discussions of the theory of spontaneous generation. Redi, the father of parasitology, in 1684 put a temporary quietus upon the uproar by describing the male and female forms of certain intestinal worms, the existence of ova and in particular by picturing the reproductive organs of *Ascaris lumbricoides*. Truth was not long triumphant in this instance and spontaneous generation remained a live topic until the time of Pasteur. Shortly after Redi, a member of the Faculty of Paris, Nicolas Andry, took up in quite serious fashion the possible relationship of worms to human pathology. So virulently was he criticized by his colleagues that he humbly withdrew his assertions, and those who had followed his lead in other medi-

cal centers of the day were likewise silenced by ridicule. Guart makes the diverting statement that this historic controversy begun in 1700 still persists in the Faculty of Paris, where, apart from the parasitologists, all must still hold as an article of faith that intestinal worms are harmless. At any rate during the latter part of the 18th and the earlier years of the 19th century, studies of the helminth parasites were confined chiefly to description and classification. A new and vital interest in their biological characteristics developed with the epoch-making researches of Steenstrup, Kuchenmeister and Leuckart, all published between 1837 and 1856. Steenstrup demonstrated, using certain intestinal worms as examples, that there exist animal species in which the descendants return to the original adult form only after two or three intervening generations of creatures which in no wise resemble their parents. Kuchenmeister and Leuckart established the existence of intermediary hosts for the cestodes. Such startling discoveries concentrated the interest of parasitologists on the problem of working out the life cycle of the various helminths. Raspail's "Natural History of Health and Disease" (1843), in which the importance of parasites in the causation of disease was strongly advocated, was granted scant attention at that epoch. It might have been expected that when Pasteur established the pathogenicity of bacteria there would have been created by the force of analogy a keener interest in the possible etiologic importance of all other parasites. Such an interest, however, was long delayed and when awakened it was directed not towards the worms but towards the protozoa in amebic dysentery and in malaria and later towards the part played by insects in the transmission of disease. The tremendous subsequent expansion of parasitology has firmly established the importance of this category of living creatures in human pathology. Helminthology has benefited from this reawakening but perhaps to a lesser extent than other subdivisions of parasitology. "New fields and pastures new" attracted the investigators and there has been comparative neglect of the worms, especially of most of the worms whose habitat in the adult stage is the human intestine. There are noteworthy exceptions, such as the extensive studies of hookworm infestation and of *Diphyllobothrium latum* anemia, but on the whole there has been least advance in the oldest field of human parasitology.

Perhaps the preoccupation with the descriptive anatomy, the classification and the details of the life cycle of these worms, which is so manifest in our textbooks, is one reason for the lack of development of detailed knowledge concerning their effect on the host. If so, one may view as encouraging the recent researches aimed at disclosing the physiologic processes of the helminths. Such studies are likely to open new vistas as to the nature of their pathogenicity.

McCoy¹ has recently published an interesting review of the work bearing on this aspect of helminthology. From his paper a few examples may be quoted of the significant results being obtained.

¹ McCoy, O. R. Physiology of the helminth parasites, *Phys. Rev.*, 1935, xv, 221-240

Respiration and Metabolism The metabolism of the three main groups of helminth parasites in the parasitic stage, under the practically anaerobic conditions of the intestines, is probably anaerobic. Energy production seems to be derived from the breakdown (fermentative?) of glycogen into carbon dioxide and fatty acids. The nature of these fatty acids varies to some extent with the species of worm, lower volatile acids and higher non-volatile acids have been identified. The production of valeric acid is most frequently mentioned. In the free living period outside the body, metabolic processes in the worm are undoubtedly aerobic.

Nutrition "Tapeworms lack a mouth and digestive tract and must absorb all their food through the surface of their body. This presumably is composed of substances already digested in the intestine and ready for absorption by the host, and probably consists mainly of sugars. Certain other groups of helminths even though they possess an intestinal tract, apparently subsist on readily absorbed substances rather than on formed substances which would require digestion. Other helminths with digestive tracts (Trematoda and Nematoda), however, have frequently been observed to contain blood corpuscles and other host tissue cells.

"It has been noticed that many helminths which are either wholly or partially embedded in a host tissue cause a necrosis and liquefaction of the tissue in their immediate neighborhood. In certain species of intestinal nematodes Hoeppli interprets the liquefaction of the mucosa around the anterior end of the worm as a form of extra-intestinal digestion in which the tissue is digested by a secretion produced by the parasite. The liquefied tissue then serves as nourishment for the worm.

"Certain intestinal nematodes belonging to the group Strongyloidea are well known blood-suckers and apparently subsist mainly on the blood of their host. The hookworm, which is the best-known example of this group, also ingests portions of intestinal mucosa detached by means of the teeth which arm the buccal cavity. Wells (1931) has recently made an interesting study of the blood sucking activities of the dog hookworm, *Ancylostoma caninum*. He operated on infected dogs under anesthesia, opened a loop of intestine without injuring the blood supply, and was able to observe directly the behavior of the worms on the intestinal mucosa. Under optimum conditions the muscular esophagus of the worms made very rapid sucking movements, sometimes at a rate as high as 120 to 250 pulsations per minute. The sucking of blood went on almost continuously, and persisted even after the posterior part of the worm had been cut off. For the most part the red blood cells passed through the intestine of the hookworm unharmed. By counting the number of corpuscles and measuring the size of the drops ejected through the anus, Wells estimated that on the average one worm would take up as much as 0.84 c.c. of the host's blood per 24 hours."

Growth There is frequent rigid restriction of parasites to certain species of hosts. The factors which determine this are not at all under-

stood. Worms are not sensitive to wide variations in environmental factors such as hydrogen-ion concentration, oxygen tension, temperature, etc. McCoy has shown that when sterile trichina larvae were introduced into the amniotic sac of rat embryos, a certain proportion were able to develop normally to the adult stage. "These experiments at least show that certain of the factors such as digestive enzymes, bacteria or their products, which are present in the normal intestinal environment, are not necessary for the development of the worms."

Reproduction In the parasitic stage the helminths guard the perpetuation of their complicated life cycle by various devices. Of these the production of an enormous number of eggs and the occurrence of hermaphroditism and self-fertilization are the most obvious. Little is known of the metabolic processes involved in this massive egg production. It is of interest that if the immunity of the host is raised by repeated reinfections the egg production of the surviving worms in the immune host will be greatly inhibited.

Secretions Evidence has accumulated that intestinal helminths produce a powerful anti-tryptic enzyme which may not only serve to protect the tissues of the parasite from the digestive juices of the host but may also, if the worms are abundant, reduce tryptic intestinal digestion.

The secretion of anti-coagulins by members of the family Strongyloidae has been known for some time. The substance appears to be related physiologically to hirudin and snake venom.

Worm tissue has been shown to possess rather weak hemolytic qualities but there is no evidence of the secretion of hemolysins. Extracts of worms are often toxic to experimental animals in the sense that when these extracts are injected disturbances of respiration, blood pressure, etc., ensue. However, there is no sound evidence of the formation of true exotoxins. It seems more likely that such "toxic" action as exists is due to the liberation of endotoxins from the bodies of dead worms. "The fact that more or less specific antibodies are developed by the host during helminthic infections has been used as an argument to support the view that worm 'toxins' may be absorbed by the host."

It seems likely that the further development of our knowledge of the physiology of intestinal helminths will furnish many leads for renewed investigations of their pathogenicity.

REVIEWS

Illustrative Electrocardiography By the late JOSEPH H. BAINTON, M.D., formerly Attending Physician and Chief of the Cardiac Clinic, Morrisania City Hospital, New York, and Consulting Physician, St. John's Long Island City Hospital, and JULIUS BURSTEIN, M.D., Associate Electrocardiographer, Morrisania City Hospital, and Cardiologist to St. Elizabeth Hospital, New York. D. Appleton-Century Co., New York. 1935. Price, \$5.00.

This is an atlas which contains examples of normal electrocardiograms and almost all of the various types of abnormal electrocardiograms. The material presented has been selected from a collection of more than 7500 curves, and it appears to be well chosen. Most of the records are good technically. The records are plainly marked to indicate the various deflections and the particular points which they illustrate. Each record is briefly described on the opposite page. The volume contains some interesting and unusual records; the curve of an infant of two days with dextrocardia is of special interest. The work is thoroughly up-to-date, containing brief discussions of coronary occlusion and Lead IV. The interpretations follow well established practice for the most part, although exception must be taken to some of them, particularly bundle branch block in the presence of complete atrio-ventricular block, and wandering, or shifting pacemaker. The chief criticism, however, concerns the brevity of the work. A presentation of the evidence upon which the various interpretations rest would materially enhance the value of the book, especially for the beginner in electrocardiography who needs more ground work than this volume offers.

P. S. B.

Osteomyelitis By ABRAHAM O. WILENSKY, M.D. 454 pages, 16 × 24 cm. The Macmillan Company, New York. 1934. Price, \$9.00.

The author has made an extensive review of the literature of osteomyelitis and presents this mass of information in an interesting manner. Moreover, he discusses the subject with a background of extensive personal experience and presents his own conclusions. In addition to the discussion of etiology, of the clinical aspects of the disease, and of therapy, there is an excellent historical summary in the introduction, and a chapter upon the anatomy of bone.

The "watchful waiting" principle of treatment is advocated in the majority of acute cases which do not show abscess pockets. It is of interest to internists to know that there is a general tendency in recent times to subscribe to this program. The exact time when to cast this policy aside is the crucial test of the surgeon's judgment and may be the critical turning point for the patient. Among surgical methods, the author prefers that of Orr which is certainly the least complicated, but has the disadvantage of producing an unpleasant odor which has almost as unfavorable a psychologic effect as the maggot treatment.

The author's rejection of the maggot treatment is based chiefly on negative facts. Though its satisfactory employment does require an exacting technic and the service of a trained staff, the maggot treatment in stubborn cases has produced results when other methods have failed. It can not be dismissed.

Likewise the author has not given all the space to the use of physical therapy, and particularly ultra-violet light, that this subject deserves. Used intelligently, these methods constitute a valuable adjunct in the therapy of bone disease.

To all those interested in this serious and unfortunately frequent form of infection, this book will serve as a valuable reference volume.

A. V.

Allergy and Applied Immunology By WARRLEN T VAUGHN Second Edition
420 pages, 15.5 × 23.5 cm C V Mosby Co, St Louis 1934 Price, \$5.00

The author in this volume has set himself the task of presenting a rather comprehensive, even though brief, view of the field of allergy in a manner designed to provide, "a handbook for the intelligent layman"

After a general consideration of the subject of allergy he discusses, in separate sections allergens, diagnosis, therapy, prognosis, the manifestations of allergy and applied immunology

Certain impressions are derived from the volume as a whole First, one feels that a patient must be of a rather high order of intelligence to completely assimilate the material presented in spite of Dr Vaughn's obvious intent to simplify the subject Unfortunately, this will probably apply to any similar attempt not because of any short-coming upon the part of the author, but rather, due to the inherent complexity of the subject under discussion A further impression gained by the reader is that the author of this volume not only knows the subject matter thoroughly but that he possesses the incalculable advantage of a smooth, clear style that immeasurably increases the "readability" of the book

The approach to the subject of allergy is particularly happy in its gradual and clear development in the mind of the reader of a background of information that renders the following chapters intelligible One may well criticize the detailed presentation of the theory of protein poisoning, elaborated by the elder Vaughn as an explanation of the phenomena of hypersensitivity, as being too dogmatic, in spite of the warning preceding it that it is simply used as a means of understanding the conditions later described There can be no criticism, however, of the author's device, designated allergic equilibrium, which is used by him to explain the interplay of the multiplicity of factors governing the allergic reactions as they occur clinically and experimentally

Section two, devoted to a consideration of the allergens, is splendid, covering this broad field briefly but comprehensively and written in a manner that is surprisingly interesting and is calculated to hold the attention of the lay reader

Space prevents consideration of each of the sections mentioned above except to say that they are given in an entirely adequate manner There is an interesting discussion of the effect of biologic grouping upon the production of symptoms On the whole, however, the reviewer feels that the subject of diet in allergy has been better handled elsewhere

In summary, one may say that while the book, in parts at least, is probably beyond the capacity of the average patient, it is excellent in itself and a valuable contribution to the literature of allergy

H M B

Manual of Physical and Clinical Diagnosis By OTTO SEIFERT and FRIEDRICH MUELLER, translated by E COWLES ANDRUS, M D xi + 561 pages, 13 × 19.5 cm J B Lippincott Company, Philadelphia 1934 Price, \$6.00

Dr E Cowles Andrus of the Johns Hopkins Medical School has made a translation of the thirty-first edition of Seifert and Mueller's well-known manual of physical and clinical diagnosis It seems likely that this small volume will now attain some of the popularity in this country that it has long enjoyed abroad It presents in clear and succinct fashion those methods of examination and such tabulated data as are most needed by the physician in practice It is astonishing how much valuable information can be condensed in a small volume In the opinion of the reviewer there is no better manual of this type available The type is not too small, the cuts are well chosen, the binding is attractive Also, the price is reasonable

T C W

The Practice of Dietetics By L HARRY NEWBURGH, M D, and FRANCIS MAC-KINNON, A B 264 pages, 22 × 15 cm The MacMillan Company, New York 1934 Price, \$4 00

This handy-sized volume will be stimulating and helpful reading to the average internist Part I, "The material needs of the organism," is full of interesting information, as well as both destructive criticism and constructive ideas It is freshly written and attempts to confine itself to facts The citation of the actual experimental basis for many of our dietetic notions adds to the interest When the reader pushes on into Parts II and III, on the selection of food and on therapy by means of diet, he realizes that the author is not attempting to furnish him with directions and diet lists for all known diseases but rather to lay down principles as to the types of diseases in which dietetic treatment is especially important and to instil sound methods of practice It is a book for students, therefore, be they undergraduates or graduates, and not a helpful quick reference volume for the practitioner

The author seems to be at one with many other recent students of obesity in going out of his way to misstate the essential problem in this condition He feels that there is no endogenous factor in obesity and believes this is shown by proving at length (elsewhere) that if the energy intake is less than the expenditure all patients will lose weight It seems an idle triumph to revindicate the law of the conservation of energy and it leaves the essential problem untouched

The chapter on the treatment of diabetes and that on renal disease (by F H Lashmet) are clear and interesting statements of the authors' methods in dealing with these two major problems

M C P

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members

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SECTIONAL MEETINGS OF COLLEGE MEMBERS

During meetings of the Board of Governors in connection with the Philadelphia Annual Session of the College, several Governors reported that they had conducted sectional gatherings of College members of their territories

Kentucky

On January 19, 1935, the Kentucky members of the College met in Louisville. Dr John Walker Moore and his associates, together with Dr J Murray Kinsman and Dr John J Moren, conducted a very interesting clinic at the Louisville City Hospital, which was followed by dinner at the Pendennis Club. The whole affair was informal and was so enjoyed that it was voted unanimously to meet in this way at least once each year. Twenty-seven out of a total of 43 Fellows and Associates were present. The next meeting will be held in Lexington at a time to be chosen later. The meeting was arranged through Dr Ernest B Bradley, former Governor of the College for Kentucky.

District of Columbia

Fellows and Associates of the College from the District of Columbia attended a local clinical assembly held at the Gallinger Municipal Hospital on Tuesday, April 16. There were four clinics of one-half hour each as follows: cardiology clinic by Dr Thomas S Lee, medical clinic by Dr Walter A Bloedorn, tuberculosis clinic by Dr Charles P Cake, neurological clinic by Dr Walter Freeman. Free discussion was encouraged. Dr William Gerry Morgan, Secretary-General of the College, gave a brief address, which was followed by a luncheon tendered by Dr Bocock, Superintendent of the Hospital. The meeting was arranged through the instrumentality of Dr Wallace M Yater, Governor of the College for the District of Columbia.

REGISTRATION STATISTICS, PHILADELPHIA (1935) SESSION, AMERICAN COLLEGE OF
PHYSICIANS

| | Member Physicians | Guest Physicians | Sr Med Students | Visiting Women | Exhib- itors | Total |
|-------------------------------|----------------------|---------------------|--------------------|-------------------|-----------------|-------|
| UNITED STATES AND POSSESSIONS | | | | | | |
| Alabama | 7 | | | 1 | | 8 |
| Arizona | 1 | | | | | 1 |
| Arkansas | 4 | 3 | | 2 | | 9 |
| California | 18 | 3 | | 5 | | 26 |
| Colorado | 8 | 1 | | 2 | | 11 |
| Connecticut | 24 | 3 | | 1 | 3 | 31 |
| Delaware | 6 | 1 | | | | 7 |
| District of Columbia | 32 | 5 | 1 | | | 38 |
| Florida | 7 | 3 | | | | 10 |
| Georgia | 8 | 1 | | | | 9 |
| Idaho | 1 | | | | | 1 |
| Illinois | 18 | 6 | | 6 | 22 | 52 |
| Indiana | 10 | 6 | | 2 | 1 | 19 |
| Iowa | 9 | 1 | | 4 | | 14 |
| Kansas | 7 | 3 | | | | 10 |
| Kentucky | 18 | | | 3 | 2 | 23 |
| Louisiana | 9 | 1 | | 2 | | 12 |
| Maine | 8 | 1 | | 3 | | 12 |
| Maryland | 27 | 4 | 1 | 5 | 2 | 39 |
| Massachusetts | 38 | 10 | | 9 | 8 | 65 |
| Michigan | 34 | 5 | | 13 | 10 | 62 |
| Minnesota | 18 | 4 | | 5 | | 27 |
| Mississippi | 3 | | | 1 | | 4 |
| Missouri | 13 | 1 | | 3 | 2 | 19 |
| Montana | 3 | | | | | 3 |
| Nebraska | 15 | 1 | | 3 | | 19 |
| New Hampshire | 2 | | | | | 2 |
| New Jersey | 49 | 12 | | 5 | 25 | 91 |
| New York | 123 | 28 | | 25 | 51 | 227 |
| North Carolina | 32 | 6 | | 8 | | 46 |
| North Dakota | 2 | | | | | 2 |
| Ohio | 53 | 14 | | 14 | 8 | 89 |
| Oklahoma | 9 | | | 3 | | 12 |
| Oregon | 3 | | | | | 3 |
| Pennsylvania | 194 | 606 | 344 | 43 | 93 | 1,280 |
| Rhode Island | 8 | | | 3 | | 11 |
| South Carolina | 3 | | | | | 3 |
| South Dakota | 1 | | | | | 1 |
| Tennessee | 7 | 1 | | 2 | | 10 |
| Texas | 14 | 1 | | 4 | | 19 |
| Utah | 2 | | | 1 | | 3 |
| Vermont | 1 | 1 | | | | 2 |
| Virginia | 28 | 3 | | 4 | | 35 |
| Washington | 3 | | | 2 | | 5 |
| West Virginia | 8 | 1 | | 2 | | 11 |
| Wisconsin | 9 | | | 3 | 3 | 15 |
| Wyoming | 2 | | | | | 2 |
| Puerto Rico | 2 | | | | | 2 |
| Philippine Islands | 1 | | | | | 1 |
| CANADA | | | | | | |
| Alberta | 1 | | | 1 | | 2 |
| Ontario | 11 | 6 | | 2 | | 19 |
| Quebec | 9 | 4 | | 2 | 1 | 16 |
| OTHER COUNTRIES | | | | | | |
| Brazil | | 1 | | | | 1 |
| China | | 1 | | | | 1 |
| Cuba | | 1 | | 1 | | 2 |
| TOTAL | 923 | 749 | 346 | 195 | 231 | 2,444 |

At the Eleventh Annual Meeting of the American Association of the History of Medicine held in Atlantic City, May 6, Dr William S Middleton (Fellow), Madison, Wis, was elected President, Dr Walter C Alvarez (Fellow), Rochester, Minn, was elected Vice-President, Dr E J G Beardsley (Fellow), Philadelphia, Pa, was elected Secretary, and Dr Carl V Weller (Fellow), Ann Arbor, Mich, was elected a member of the Council

During the meeting, Dr Harlow Brooks (Fellow), New York City, presented an historical paper entitled "A Navajo Medicine Song," and Dr Walter C Alvarez (Fellow), Rochester, Minn, presented a paper entitled "Folklore a Physician Should Know"

Dr Howard T Karsner (Fellow), Professor of Pathology in the Western Reserve University, Cleveland, Ohio, was recently elected to membership in the *Association Française pour l'Etude du Cancer*, the French Association for the Study of Cancer

The 1935 Graduate Fortnight of the New York Academy of Medicine will be held October 21 to November 2, and will be devoted to a consideration of diseases of the respiratory tract Eighteen important hospitals will present coordinated afternoon clinics and clinical demonstrations At the evening meetings, prominent clinicians from various parts of the country will discuss various aspects of the general subject Among Fellows of the College who will be speakers at the evening meetings are Drs James Alex Miller, Jonathan C Meakins, J Burns Amberson, George Blumer, Henry Chickering, Maximilian A Ramirez and David Riesman

Under the Presidency of Dr Samuel E Munson (Fellow), Springfield, Ill, the District Medical Society of Central Illinois held its Sixty-First Annual Meeting at Springfield on April 17 Among others who presented papers were Dr Walter L Bierring (Fellow), President of the American Medical Association, and Dr Andrew C Ivy (Fellow) Head of the Department of Physiology and Pharmacology of Northwestern University Medical School

The Sixth Annual Staff Demonstration Week of the Hackensack (Hackensack, N J) Hospital was conducted April 15 to 19, under the direction of its Medical Board, on which Dr Herman Trossbach (Fellow) is Director of Medicine and Dr Richard E Knapp (Fellow) is Director of X-Ray Dr Trossbach presented a demonstration on artificial pneumothorax in the treatment of lobar pneumonia, and Dr Richard E Knapp discussed the x-ray interpretations Dr George M Levitas (Fellow) contributed to the pediatric program a paper on "Prevention of 'Physiological' Weight Loss in the New Born"

Dr Henry Wallace (Fellow), New York City, was the guest of honor and speaker at the Annual Alumni Luncheon of the Long Island College Hospital, Brooklyn, recently His topic was "Memoirs of an Old Timer" Dr Wallace was a member of the class of 1890 He became a Fellow of the American College of Physicians in 1920

The Mississippi State Board of Health, through its Executive Officer, Dr Felix J Underwood (Fellow), has engaged in a program of radio talks for the purpose of disseminating information on preventive medicine and public health policies to the citizens of that State

Dr Ralph H Kulins (Fellow), Chicago addressed the Miami Valley Hospital Society at Dayton, Ohio, May 3, on "Fever Therapy for Dementia Paralytica"

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